# DEVELOPMENT AND EVALUATION OF FELODIPINE EXTENDED RELEASE TABLET FORMULATION

**Dissertation submitted to**

**THE TAMILNADU DR. MGR MEDICAL UNIVERSITY, CHENNAI-32**

***In partial fulfillment for the award of the degree of***

**MASTER OF PHARMACY**

**IN**

**PHARMACEUTICS**

***Submitted by***

**Register Number: 261210001**

**UNDER THE GUIDANCE OF**

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All India Council for Technical Education. New Delhi.

# THE CERTIFICATE

This is to certify that the dissertation work entitled **"DEVELOPMENT AND EVALUATION OF FELODIPINE EXTENDED RELEASE TABLET FORMULATION"** submitted to **THE TAMILNADU DR. MGR MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree **"MASTER OF PHARMACY" in Pharmaceutics** is a bonafide research work done by **Register Number: 261210001,** under my Guidance in the Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600 097 during the academic year 2013-2014.

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# DECLARATION

I do hereby declare that the thesis entitled **"DEVELOPMENT AND EVALUATION OF FELODIPINE EXTENDED RELEASE TABLET FORMULATION"** has been originally carried out by **Reg No: 261210001** under the supervision and guidance of **A.Sathish Babu,M.Pharm** (Industrial guide) and **Dr.R.Kumaravelrajan,M.Pharm.Ph.D.,** (Institutional Guide), Department of Pharmaceutics, C.L.Baid Metha college of Pharmacy,Chennai-97 during the academic year 2013-2014.

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# ACKNOWLEDGEMENT

It is a great time for me to acknowledge those without whom, this work would not have been fruitful.

It gives me an immense pleasure in expressing my deep sense of gratitude to my respected guide **DR.R.Kumaravelrajan**,**M.Pharm.,Ph.D,** Department of Pharmaceutics**,** C.L.Baid Metha college of pharmacy for his remarkable guidance, constant encouragement and every scientific and personal concern throughout the course of investigation and successful completion of this work.

I express my deep heartful and sincere thanks to my industrial guide **A.SathishBabu,M.Pharm, Formulation research and development, The Madras Pharmaceutical limited, Chennai-97,** for allowing me to accomplish the project work.

It is great pleasure and honor for me to owe gratitude to **Dr. Grace Rathnam, M.Pharm, Ph.D**., principal for all her support and for giving a valuable guidance and scientific support to carry out this work.

I express my wholehearted gratitude and I would like to extend my appreciation to **Mr.Malai, Mr.Karthick and Mr.Ilayaraja, FR&D Department, The Madras Pharmaceuticals, Chennai-97** for their valuable advice and cooperation in bringing out this project.

I express my deep sense of thanks to **Mr.Sathish kumar and Mr. Hemachandar, AR&D Department, The Madras Pharmaceuticals, Chennai-97** for their guidance, indefatigable support and constant encouragement for the entire period of my thesis work.

I feel proud to express my hearty gratitude and appreciation to all my Teaching and Non-teaching Staff members of **C.L. Baid Metha College of Pharmacy Chennai-97** who encouraged to complete this work.

I feel proud to express my hearty gratitude to all my friends. Also I want to thank all of those, whom I may not be able to name individually, for helping me directly or indirectly.

I thank the God and My beloved family for showering their blessings for the completion of my thesis work.

I dedicate this dissertation work to my family who have supported and helped me to greatest possible extent.

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**(Register Number: 261210001)**

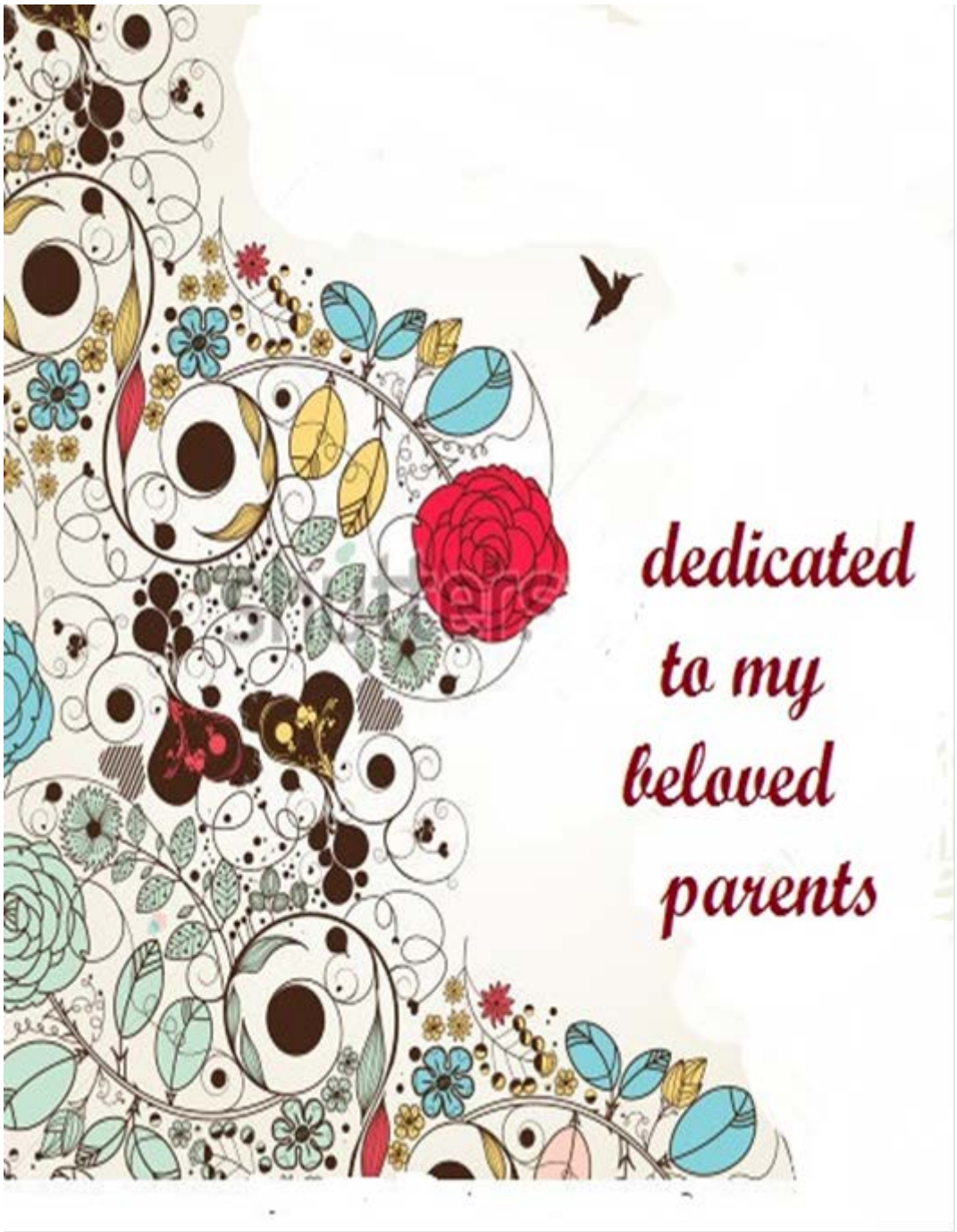
# List of Abbreviations

| | |
|---|---|
| API | Active Pharmaceutical Ingredient |
| USP | United States Pharmacopoeia |
| CR | Controlled Release |
| ER | Extended Release |
| EC | Ethyl Cellulose |
| HPMC | Hydroxy Propyl Methyl Cellulose |
| IPA | Isopropyl Alcohol |
| HCL | Hydrochloric Acid |
| MCC | Microcrystalline Cellulose |
| FTIR | Fourier Transform Infrared Spectroscopy |
| PEG | Poly Ethylene Glycol |
| MEC | Minimum Effective Concentration |
| HPLC | High Performance Liquid Chromatography |
| UV | Ultra Violet |
| ICH | International Conference On Harmonization |
| NMT | Not more than |
| NLT | Not less than |
| RT | Room temperature |
| AUC | Area under curve |
| $V_d$ | Volume of distribution |
| SD | Standard deviation |
| Fig | Figure |
| Avg. wt | Average weight |

# Nomenclature

| | |
|---|---|
| % | Percentage |
| Conc | Concentration |
| Hr | Hour |
| Rpm | revolution per minute |
| w/w | weight/weight |
| $Kg/cm^2$ | Kilogram/square centimeter |
| µg/ml | microgram / milliliter |
| Sec | Seconds |
| g/ml | gram / milliliter |
| Nm | Nanometer |
| Mm | Millimeter |

# CONTENTS


dedicated
to my
beloved
parents

# 1. Introduction

Over the past 30 years, as the expenses and complications involved in marketing a new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. These factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems.

The goal of designing sustained or controlled drug delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.[1]

## *1.1 Oral drug delivery:*[2]

This is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process.

For the past decades, there has been enhanced demand for patient compliance dosage forms. As a result the demand for the technologies has been increased three fold annually. Since the development cost of new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration. It has wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms is difficult to solve.

## *1.2 Modified Drug Delivery system:*[3]

Dosage forms can be designed to modify the release of drug over a given time or after the dosage form reaches the required location. Drug release acquire only after sometime of the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment or to increase patient compliance and convenience of administration.

### 1.2.1 Physicochemical properties of the drug:[4]

Several physicochemical properties of the active drug can influence the choice of dosage form. This include aqueous solubility and stability, partition coefficient (or, more appropriately, permeability values) and salt form. The aqueous solubility and intestinal permeability of drug compounds are of paramount importance. A classification has been made whereby drugs can be considered to belong to one of four categories:

- High solubility and high permeability (best case)
- Low solubility and high permeability
- High solubility and low permeability
- Low solubility and low permeability (worst case).

This is now codified as the Biopharmaceutical Classification. Consider first the influence of solubility. A drug that is highly soluble at intestinal pH and absorbed by passive diffusion (i.e. not site-specific absorption) would probably present the ideal properties for inclusion in a modified release dosage form.

Drug compounds that satisfy the solubility and permeability requirements should also ideally have:

- A biological half-life of between two and six hours so that accumulation in the body does not occur a lack of capability to form pharmacologically active metabolites by, for example; first-pass metabolism.

- Modified release is actually used for drugs, which undergo first-pass metabolism but this should not be to such an extent that only inactive metabolites are left after absorption.

- A dosage not exceeding 125-325 mg in order to limit the size of the delivery system.

- The factors that influence the rate and extent of absorption depend upon the route of administration the intravenous route offers direct access to the systemic circulation and the total dose administered via this route is available in the plasma for distribution into other body tissues and the site(s) of action of the drug. Other routes will require an absorption step before the drug reaches the systemic circulation. Factors affecting this absorption will depend on the physiology of the administration site(s) and the membrane barriers present at those site(s) that the drug needs to cross in order to reach the systemic circulation.

### 1.2.2 Biopharmaceutical principles of drug delivery:[5]

The Rate and extent of drug absorption into the systemic circulation, a schematic illustration of the steps involved in the release and absorption of a drug from a tablet dosage form. It can be seen from this that the rate and extent of appearance of intact drug in the systemic circulation depends on a succession of kinetic processes. The slowest step in this series, which is known as the rate-limiting step controls the overall rate and extent of appearance of intact drug in the systemic circulation. The particular rate-limiting step will vary from drug to drug. For a drug, which has a very poor aqueous solubility the rate at which it dissolves in the gastrointestinal fluids is often the slowest step, and the bioavailability of that drug is said to be dissolution-rate limited.

In contrast, for a drug that has a high aqueous solubility its dissolution will be rapid and the rate at which the drug crosses the gastrointestinal membrane may be the rate-limiting step (permeability limited). Other potential rate-limiting steps include the rate of release of the drug from the dosage form (this can be by design in the case of controlled- release dosage forms), the rate at which the stomach empties the drug into the small intestine, the rate at which the drug is metabolized by enzymes in the intestinal mucosal cells during its passage through them into the mesenteric blood vessels, and the rate of metabolism of drug during its initial passage through the liver, often termed the 'first-pass' effect.

## *1.3 Classification of Modified Release Drug Delivery:[6]*

Modified Release dosage form may be classified as

- Extended release
- Sustained release
- Controlled release
- Delayed release
- Site specific targeting
- Receptor targeting

### 1.3.1 Extended Release:

The term controlled/extended release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue.

The oral route of administration for extended release systems has received greater attention because of more flexibility in dosage form design. The design of oral extended release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Extended release denotes that the system is able to provide some actual therapeutic control whether be it of temporal or spatial nature or both. In other words, the system attempts to provide a constant drug concentration in the target tissue.

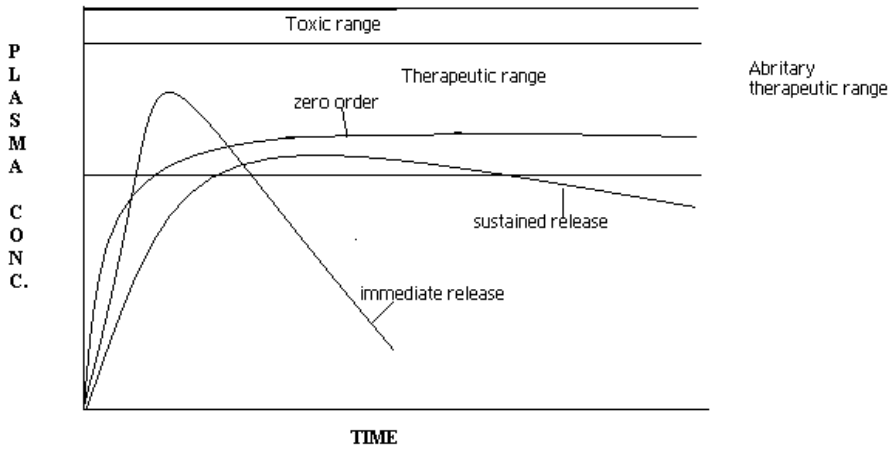



**Fig 1: Plasma level versus time profile showing difference between controlled release, sustained release and release from conventional dosage forms.**

### 1.3.2 Advantages of Extended Release Dosage forms:[7]

- **Improved patient compliance** and convenience due to less frequent drug administration.
- **Reduction in fluctuation** in steady state levels and therefore, better control of disease condition and reduction intensity of local or systemic side effects.
- **Increased safety margin** of high potency drugs due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.
- **Reduction in health care costs** through improved therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.
- **Attenuation of adverse effect**, the use of extended release products avoids the high initial blood concentration, which may cause many side effects like nausea, local irritation, hemodynamic changes etc.

### 1.3.3 Disadvantages of Extended Release Dosage form:

- Toxicity due to dose dumping.
- Increased cost.
- Unpredictable and often poor *in vitro- in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).

- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.
- Increased potential for first-pass clearance.

### 1.3.4 Ideal candidate for Extended/controlled Release Drug Delivery systems:[8]

The desired biopharmaceutical characteristics of drugs to be used in the development of oral controlled release dosage forms are:

**Table 1: Parameters for drug selection**

| **Parameters for drug selection** | |
|---|---|
| **Parameter** | **Preferred value** |
| Molecular weight | <1000 |
| Solubility | >0.1mg/ml for pH 1to pH7.8 |
| Apparent partition coefficient | High |
| Absorption mechanism | Diffusion |
| General absorbability | From all GI segments |
| Release | Should not be influenced by pH and enzymes |

**Less protein binding**

To evaluate whether a drug is viable candidate or not for the design of *per oral* CR formulation, one must consider the following pharmacokinetic parameters of the drug.

**Elimination half-life :** Preferably between 0.5& 8 hours

**Total body clearance :** Should not be dose dependent

**Absolute bioavailability :** Should be 75% or more

**Absorption rate :** Must be greater than release rate

**Therapeutic concentration :**

The lower the $c_{ss}^{av}$ and the smaller the $v_d$ ,the lesser is the amount required.

**Apparent volume of distribution ($V_d$):**

The larger the $v_d$ and Minimum Effective Concentration (MEC), the larger will be the dose size required. The maximum dose to be incorporated in to a *per oral* Controlled release (CR) formulations is about 500mg. The smaller the $v_d$, the easier is incorporation of drug in to dosage form.

**Minimum toxic concentration (MTC):**

Apart the values of MTC and MEC, safer the dosage form and also suitable for drugs with very short $t^{1/2.}$

### *1.3.5* Factors influencing oral extended release dosage design:[9]

#### 1.3.5.1 Biological Factors

**A. Biological Half Life:**

The usual goal of an oral extended release product is to maintain therapeutic blood levels over an extended period. Therapeutic compounds with short half-lives are excellent candidates for sustained release preparation, since this can reduce dosing frequency. However this is limited. In general, drugs with half-lives shorter than 2 hrs, such as furosemide or levodopa are most candidates for sustained release preparations. Compounds with long half-lives, more than 8hrs are also generally not used in sustained release forms, since their effect is already sustained. Digitoxin, warfarin, and phenytoin are some examples.

**B. Absorption:**

The characteristic of absorption of a drug can greatly affect its suitability as a extended-release product. Since the purpose of forming an extended- release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs and devices in the absorptive areas of GI tract is about 8-12hrs, the maximum half-life for absorption should be approximately 3-4hrs;otherwise,the device will pass out of the potential region before absorption is complete. If a drug is absorbed by active transport or transport is limited to a specific region of the intestine, sustained release preparations may be disadvantageous to absorptions.

**C. Metabolism:**

Drugs that are significantly metabolized before absorption, either in the lumen or the tissue of the intestine can show decreased bioavailability from slower releasing dosage forms. Eg, Aloprenol was most extensively metabolized in the intestinal wall when given as a sustained release preparation. High concentration of dopa-decarboxylase in a intestinal wall will result in a similar effect for levodopa. If levodopa is formulated in a dosage form with a drug compound that can inhibit the dopa-carboxylase enzyme, the amount of levodopa available for absorption increase and can sustain its therapeutic effects. Formulation of these enzymatic ally susceptible compounds as prod rugs is another viable solution.

### 1.3.5.2 Physiochemical Factors Influencing Oral Extended-Release Dosage Form Design:[10]

**A. Dose size:**

For orally administered system, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0gm is considered maximal for the conventional dosage form. This also holds for sustained –release dosage form, those compound that require a large dosing size can sometimes can be given in multiple amounts or formulated into liquid systems. Another consideration

is the margin of safety involved in administration of large amounts of drug with narrow therapeutic range.

**B. Ionization, pKa and Aqueous Solubility:**

Most drugs are weak acids or bases. Since the unchanged form of drug preferentially permeates across lipid membrane, the drug in an unchanged form is advantageous for drug permeation. Consider a drug for which the highest solubility is in the stomach and is unchanged in the intestine. For conventional dosage form, the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of intestine. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form meaning that the solubility of the drug may change several orders of magnitude during its release. Compounds with very low solubility (<0.01 mg/ml) are inherently sustained. The drugs that are limited in absorption by the dissolution rate are digoxin, griseofulvin and salicylamide. The lower limit has been reported to be 0.1mg/ml.

**C. Partition coefficient:**

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect these membranes are lipid in nature .Therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Compounds with a relatively high partition coefficient are predominantly lipid soluble and consequently, have very low aqueous solubility. Phenothiazine are representative of this type of compound.

**D. Stability:**

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability

when administered from a sustaining dosage forms. This is because more drugs is delivered in the small intestine and hence it is subject to degradation. Propantheline, probanthine are representative examples of such drugs.

### 1.3.6 Unsuitable candidates for Extended-Release dosage forms:

Short elimination biological half-life (< 2hrs).E.g. penicillin G, Furosemide

Long elimination biological half-life (>12hrs).Eg; Diazepam, Phenytoin

Narrow therapeutic index. Eg; Phenobarbital, Digitoxin

Not effectively absorbed in the lower intestine Eg; Riboflavin, Ferrous salts

Large dose (>1g) Eg; Sulphonamides.

## *1.4 Types of tablet manufacturing:*[11]

**Granulation:**

### 1.4.1 Wet granulation:

Wet granulation involves addition of solution to blended powder and mixing is done at a predetermined period of time and at specified speed. After this process is complete, the wet mass is milled and dried on a tray drier on to which the mass is spread.

### 1.4.2 Dry granulation:

Dry granulation involves (roll compaction or slugging) involves the compaction of powders at high pressures into large, often poorly formed tablets or compacts. These compacts are then milled and screed to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of heat and moisture in the processing. Dry granulation can be produced by extruding powders between hydraulically-operated rollers to produce thin cakes that are subsequently screed or milled to give the desired granule size.

### 1.4.3 Direct compression:

Direct compression is used when a group of ingredients are to be blended and placed onto a tablet press to be made into a perfect tablet without changing any of the ingredients. Powders that can be blended and compressed are commonly referred to as directly compressible or as direct-blend formulations.

## *1.5 Methods to retard the drug release*[12]

It can be classified as follows:

- Reservoir system including

  Enteric coated tablets, capsules, coated granules and microcapsules.
- Osmotic systems
- Ion-exchange resins
- Matrix systems

### 1.5.1 Matrix Systems

**Definitions:**

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipient in order to achieve release by a continuous leaching of the drug from the inert matrix core.

Drug release from the bulk of matrix involves two matrix mechanisms:

1) The Erosion rate of the matrix determines the drug release state in matrices governed by erosion or dissolution.

2) The diffusion through a barrier membrane describes drug release in insoluble coating via fick's second law of diffusion.

**Table 2: Materials used as retardants in matrix Tablets**

| Nature of the polymer | Examples |
|---|---|
| **Insoluble, Inert** | Poly Ethylene, Polyvinylchloride, Ethyl Cellulose and Methyl acrylate |
| **Insoluble, Erodible** | Carnaubawax,Stearylalcohol,Stearicacid, Polyethylene Glycol and Triglycerides. |
| **Hydrophilic** | Methyl Cellulose, Hydroxy Ethyl Cellulose Hydroxy propyl Methyl Cellulose, Xanthan gum, Sodium alginate and Chitosan. |

### 1.5.2 Drug Release from Matrix Systems:[13]

**Mechanism of drug release from swelling controlled release systems**

**Polymer swelling and drug release:**

The overall drug release mechanism from swelling controlled release systems based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system. When a matrix comes in contact with an aqueous solution, wetting occurs first at the surface and then progresses by way of microscopic pore spaces into the matrix.

The excipient in the matrix also absorb water, hydrates and swells to block up the existing pores, dissolves the content to create a more porous structure, gels to form a more viscous solution giving rise to positive pressure opposing liquid entry or causes disintegration of the matrix . Before a liquid can enter a matrix, there must be a driving force, which is derived from the pressure difference. The rate of liquid penetration into the matrix is determined by balance of this force promoting fluid entry towards the interior and the viscous force opposing it, which soon develops as soluble excipients in matrix dissolve or swell.

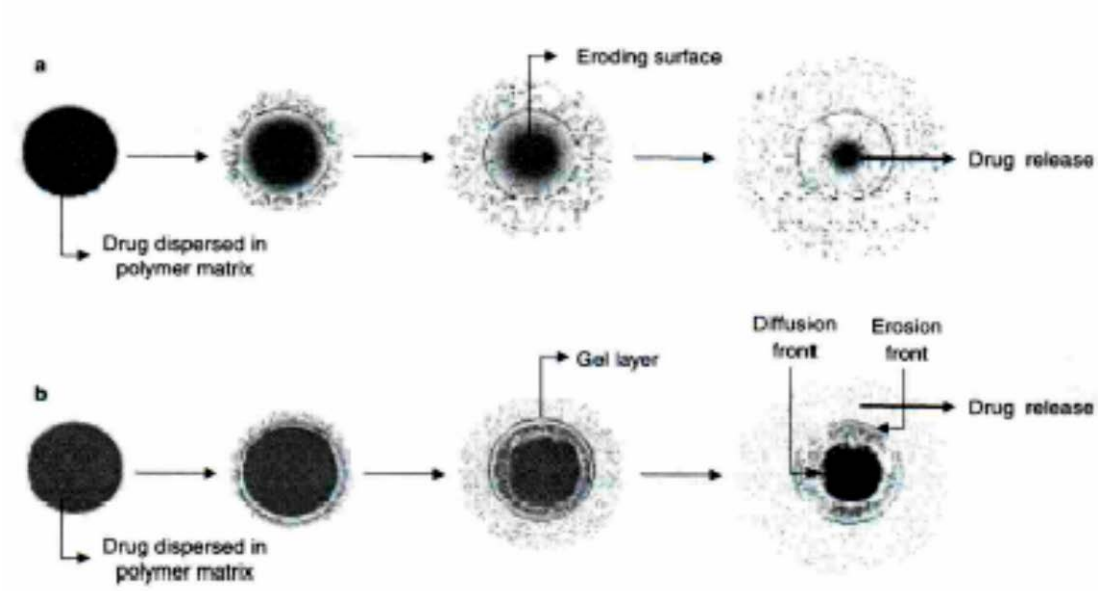



**Fig 2: (a) Drug release controlled by polymer erosion; (b) Drug release controlled by swelling and erosion**

The swelling of the matrix and consequent drug release by diffusion from the matrix and erosion of the matrix is shown in Figure 2a and 2b.

A hydrophilic matrix, controlled-release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away. The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer **(Fig: 3**). Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion.[14]

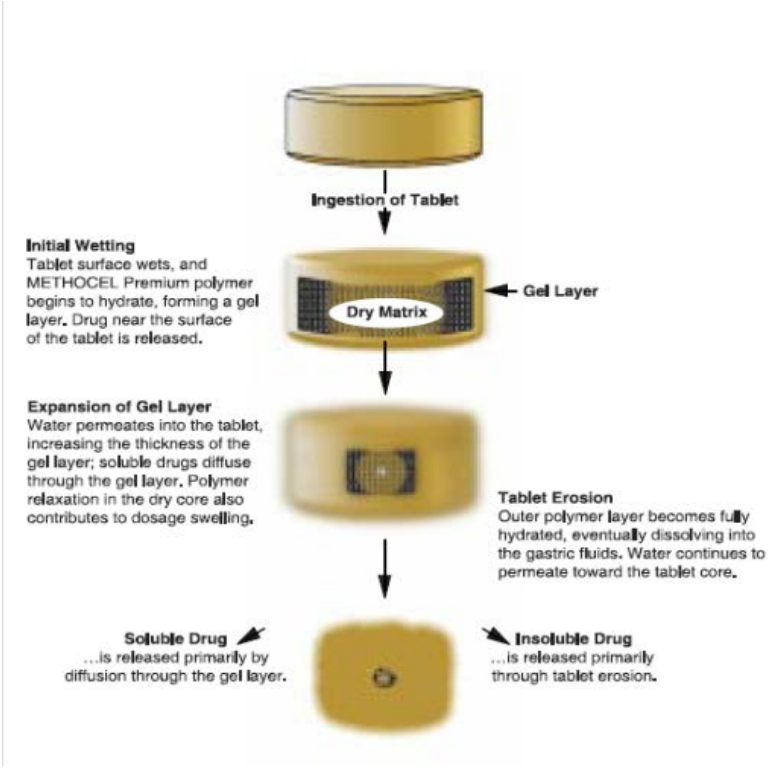



**Fig 3: Mechanism of drug release from matrix gel forming tablets**

### *1.6 Pharmaceutical coating processes:*[15]

Basically there are five major techniques for applying coatings to pharmaceutical solid dosage forms:

1. Sugar coating
2. Film coating
3. Enteric coating
4. Fluid bed or suspension coating
5. Compression coating

### 1.6.1 Film coating

Film coating is a process that involves the deposition of thin but uniform, polymer film onto the surface of the core tablet. The polymeric substance most

commonly used is Hydroxyl Propyl Methyl Cellulose, Hydroxyl Ethyl Cellulose. The film coating protects the medicament from the atmospheric effects. By its composition the coating is designed to rupture & expose the core tablet at the desired location within GIT.

### 1.6.2 Advantages

- Minimal weight increase (typical 2 to 3% of tablet core weight)
- Significant reduction in processing times
- Increased process efficiency and output
- Increased flexibility in formulation
- Cost effectiveness
- Acceptable for diabetic patients

**Table 3: Reasons for Film coating**

| | |
|---|---|
| Appearance | To change the color, for branding purposes. |
| Stability | To protect the active ingredient from moisture, light and/or the acidic environment of the stomach |
| Taste/odor masking | To provide an easy to swallow tablet without the bitter taste of many actives |
| Release characteristics | Many film coating materials have functional properties which enable the delayed(enteric)release of dosage forms |

### 1.6.3 Components required for film coating formulations: [16]

**1. Polymer:**

Usually cellulose derivatives, acrylic and copolymers are used.

**Non enteric polymers:** E.g. Hypermellose, HydroxyEthylCellulose, polyethylene glycol, Ethyl Cellulose, Hydroxyl propyl Cellulose.

**Enteric polymer:** E.g. Cellulose acetate phthalate, polymethacrylates, polyvinyl acetate phthalate.

**2. Plasticizer:**

Some of the commonly used plasticizers are castor oil, propylene glycol, polysorbates and organic acid esters.

**3. Colorants:**

Colorants are used to provide distinctive color and elegance to a dosage form. Colorants can be classified into 3 classes.

Organic dyes example: Sunset yellow, Tartrazine, Erythrosine.

Inorganic colours example: Iron oxide red, yellow, Titanium dioxide, Talc.

Natural colours example: riboflavin, carmine.

**4. Solvents:**

The primary function of a solvent system is to dissolve or disperse the polymers and other additives and convey them to the substrate surface. The most widely used solvents for enteric coating polymers are water, ethanol, isopropanol, chloroform, acetone etc.

## *1.7 Hypertension:*[17]

Hypertension, or high blood pressure, is a medical condition in which the blood pressure is chronically elevated, mainly arterial hypertension.

**Hypertension can be classified as**

1. Essential hypertension indicates that no specific medical cause can be found to explain a patient's condition.

2. Secondary hypertension indicates that the high blood pressure is a result of (i.e. secondary to) another condition, such as kidney disease or certain tumors (especially of the adrenal gland).

### 1.7.1 Blood pressure:

It is defined as the lateral pressure exerted by blood on blood vessels. The blood pressure which is normally expressed is arterial blood pressure.

It has two phases:

1. **Systolic blood pressure:** it is the maximum blood pressure. This occurs during the systole of the heart (range 100-120mm hg).

2. **Diastolic blood pressure:** it is the minimum pressure. It is occurs during the diastole of the heart (range 60-80mm hg).

**Blood pressure ranges:**

| | | |
|---|---|---|
| Normal blood pressure | : | Below 120 mm Hg / 80mm Hg |
| Pre hypertension | : | 120-139 mm Hg / 80-89 mm Hg |
| Mild Hypertension (Stage 1) | : | 140-159 mm Hg / 90-99 mm Hg |
| Moderate-Severe Hypertension | : | Higher than 160-100 mm Hg |

The systolic pressure corresponds to the pressure in the arteries as the heart contracts and pumps blood forward into the arteries. The diastolic pressure represents the pressure in the arteries as the heart relaxes after the contraction. The diastolic pressure reflects the lowest pressure to which the arteries are exposed. The pressure exerted by blood within the artery is shown in **Fig: 4**

An elevation of the systolic or diastolic blood pressure increases the risk of developing cardiac disease, renal disease, arteriosclerosis, eye damage and stroke. These complications of hypertension are often referred to as end-organ damage because damage to these organs is the end result of chronic high blood pressure .For that reason, the diagnosis of high blood pressure is important so efforts can be made to normalize blood pressure and prevent complications. Hypertension is clearly a major public health problem.

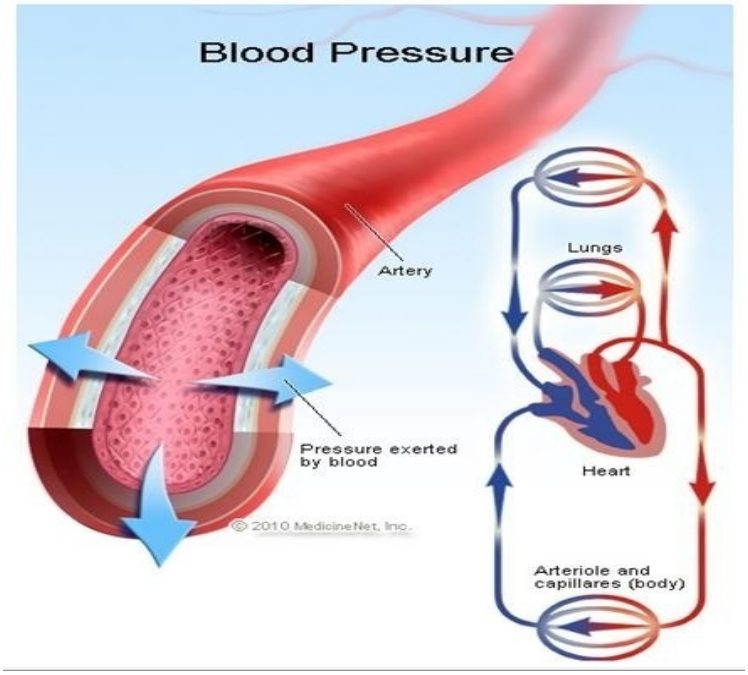



**Fig 4: Blood pressure within the artery**

### 1.7.2 Factors affecting blood pressure:[18]

- Blood volume and cardiac output
- Peripheral resistance
- Elasticity of blood levels
- Diameter of lumen of blood vessels
- Viscosity of blood

### 1.7.3 Mechanism of calcium effect of blood pressure

During each heart beat, a relatively small amount of calcium enters inside across the sacrolemma during the action potential and more calcium needed for muscle activation is released from the sacroplasmic reticulum. This release is triggered by calcium influx across the sacrolemma. The intracellular calcium concentration increase and brings about muscle contraction (systolic) through bridges cycle. Following this calcium is reaccumulated into the sacroplasmic reticulum by calcium pumps. This causes relaxation of the muscle (diastole).

### 1.7.4 Calcium channel blockers:

Calcium channel blockers are class of drugs and natural substances which disrupt the conduction of calcium channels. It has effects on many excitable cells of the body, like the muscle of the heart, smooth muscles of the vessels or neuron cells. The main action of calcium channel blockers is to decrease the blood pressure and is mainly prescribed for the treatment of hypertension. Calcium channel blockers interfere with the entry of calcium into myocardial and vascular smooth muscle. This decreases the availability of intercellular calcium. The three channels of calcium transport are:

**1. Voltage dependent channel:**

It opens and closes in response to a voltage gradient. Calcium channel blockers close this gate. This inhibits the entry of extracellular calcium.

**2. Receptor operated channel:**

This is activated by alpha adrenergic agonist or angiotensin. This channel also blocked by calcium channel blockers.

**3. Sodium channel exchange:**

It is important only for the action of cardiac glycosides.

Example of calcium channel blockers include, nifedipine (Procardia), diltiazem (Cardizem), verapamil (Isoptin,Calan), nicardipine (Cardene), amlodipine (Norvasc), and felodipine (Plendil).

**Effect on peripheral blood vessels:**

Calcium channel blockers relax the vascular smooth muscle in systemic as well as pulmonary arterial circulations. The decrease the vascular resistance and the blood pressure in both the territories. They have been used with beneficial effect in the treatment of systemic and pulmonary hypertension.

### 1.7.5 Important actions of calcium channel blockers are:

- Antiarrhythmic effect
- Negative ionotropic effect which decreases cardiac contractility
- Dilatation of coronary arteries
- Relaxation of peripheral blood vessels
- Antianginal effect

### 1.7.6 Function of calcium antagonists:[19]

- Block calcium entry by preventing opening of voltage-gated L-type calcium channels.
- Mainly affect heart and smooth muscle, inhibiting the calcium entry caused by depolarization in these tissues.
- Selectivity between heart and smooth muscle varies; verapamil is relatively cardio selective; felodipine is relatively smooth muscle-selective, and diltiazem is intermediate.
- Vasodilator effect is mainly on resistance vessels, reducing after load.

- Calcium antagonists dilate coronary vessels, which is important in variant angina.
- Effects on heart (verapamil, diltiazem):antidysrhythmic action(mainly atrial tachycardia),because of impaired atrioventricular conduction; reduced contractility.
- **Clinical uses**

  Antidysrhythmic (mainly verapamil)

  Angina (e.g. diltiazem)

  Hypertension (mainly dihydropyridines)

### *1.8 Angina pectoris:*

Angina is a symptom of a condition is called myocardial ischemia. It occurs when the heart muscle (myocardium) doesn't get as much blood and hence as much oxygen as it requires.

**Antianginal property of calcium channel blockers:**

These drugs are probably due to (1) improvement in the coronary blood flow and (2) decrease in the oxygen demand of the heart due to reduction in systemic vascular resistance (vasodilatation) and blood pressure (arterial).

# 2. Literature Review

- **Hardik Rana et al.,(2013)[20],** The extended release tablets were prepared by direct compression method and formulated using different polymer ratios. Hydrophilic polymers like Hydroxypropyl methylcellulose K15M (15-35%) and hydrophobic polymer like Kollidon SR (10-305%) were used. The results of dissolution studies indicated that formulation F2 (KSR-40mg and HPMC-50mg) and F7 (KSR-60mg and HPMC-30mg) exhibited drug release pattern very close to innovator release profile. From that F10 (KSR-50mg and HPMC-50mg) was prepared, exhibited same release profile to that of innovator product. From the experimental data, an optimal formulation was developed which has proved to be similar with the dissolution profile of the chosen innovator product and which was protected against light and moisture by opadry seal coat and sunset yellow.

- **Zhao Xia.,et al.,(2013),[21]** To evaluate the bioequivalence of the two felodipine extended release tablets in healthy male subjects. Methods A single oral dose 5 mg of test and reference felodipine extended release tablets were given to 24 subjects according to an open randomized crossover design. The concentrations of felodipine in plasma were determined by LC-MS/MS. The pharmacokinetic parameters were calculated and the bioequivalence was compared. The 90% confidential interval of Cmax,AUC0-72h and AUC 0-∞ of tested formulation were 109.6%~141.6%,99.2%~120.2 % and 96.2%~117.8%. There was no statistically significant difference in parameters $T_{max}$ between the two preparations. The relative bioavailability of felodipine of test preparations was (114.0±33.7) %.The two preparations were bioequivalent.

- **Kumar, P. Santhosh; Rao,V.Srinivasa ; et al.,(2012)**[22]A rapid and reproducible High Performance Liquid Chromatographic method has been developed for the estimation of Felodipine in its pure form as well as in pharmaceutical dosage forms. Chromatography was carried out on an Symmetry C18 column (25cm × 4.5mm, 5µ), Isocratic elution was carried with the mobile phase acetonitrile and water (80:20 v/v) at flow rate of 1ml/min. and the detection was done at 234 nm was developed and fully validated for the determination of Felodipine. The retention time of the drug was 3.617 min. Initially a method was developed and partially validated with parameter such as LOD & LOQ, linearity, accuracy and precision etc. Results obtained from this study indicates that the method is showing perfect linearity in the range of 25 to 200 µg/ml. LOD and LOQ were found to be 0.125 and 1.25 ng/ml , respectively. Our result from the present study also indicates that the tested plendil contains 96.6% of Felodipine drug and passed QC successfully.

- **Kunal P. Pagar et al.,(2012)**[23] The research work deals with the development of a time delayed chronotherapeutic formulation of felodipine (FD) aimed at rapid drug release after a desired lag time in the management of hypertension. This dissolution enhancement and rapid drug release resulted from FD amorphisation, as confirmed by XRD, DSC and SEM studies. FTIR and 1H NMR studies confirmed the complex formation between FD and cyclodextrin based on the observed hydrogen bond interactions. Influence of formulation variables like polymer viscosity, plasticizer concentration, super disintegrant concentration in the swellable layer and percent coating weight gain was investigated to characterize the lag time. Upon permeation of water, the core tablet swelled, resulting in the rupture of the coating layer, followed by rapid drug release. The developed formulation of FD showed a lag time of 5-7 h, which is desirable for chronotherapeutic application.

- **Hsiao chia-ling et al., (2011)[24],** The objective of this study was to investigate the pharmacokinetics of felodipine in healthy male Taiwanese subjects. The subjects received 5 mg (n = 80) or 10 mg (n = 20) of Plendil® (felodipine extended-release tablets; felodipine ER) once daily for 6 days. Compared to data from the literature, the mean $C_{max,\ ss}$ and $AUC_{\tau}$ of 5 mg felodipine in healthy young Taiwanese subjects were similar to or slightly lower than data from Swedish, Danish, Turkish and Canadian studies in healthy young subjects who received 10 mg felodipine. Comparable $C_{max}$ values and approximately 30% lower AUC values were observed when comparing the 5 mg Taiwanese data to data in healthy elderly German subjects who also received 5 mg felodipine. Taiwanese subjects might have lower CYP3A4 activity to metabolize felodipine, which is similar to the phenomenon observed with nifedipine.

- **V.Sreedevi, Puttarajesh kumar et al., (2011)[25],**The investigation was aimed to study bioequivalence of two felodipine formulations and pharmacokinetic studies of human plasma were conducted. Pharmacokinetic parameters such as Cmax, Tmax, AUC (0-t), AUC(0-∞), and t½ were calculated and the blood plasma level data of the reference product and the test product were compared. Plasma onset of drug for both was 0.5 hr. The Cmax for reference product was 10.72 1.15 ng/ml with Tmax of 3.17 0.7hr. The Cmax and Tmax of the Felodipine test product were 10.70 1.17 ng/ml and 3.75 0.44 hr. The AUC(0-t) for reference product was 216.24 33.66 ng.h / ml and 196.50 30.28 ng.h / ml for the test product. Based on the above observations it could conclude that the test product is bioequivalent of that of the reference product of felodipine and both are well tolerated. Further the results of the present investigation shown that there is scope for further studies on felodipine metabolism with respect to efficacy and pharmacokinetics.

- **Rares.I, Iovanov,et al.,(2009)[26],**In this paper we have studied the influence of some variables on the release of felodipine from extended release hydrophilic matrix tablets. The employed polymers for the extension of the release were: hydroxypropyl methyl cellulose (Methocel E4MCR and Methocel K100M) and polyethylene oxide (PolyoxWSR Coagulant). For this purpose, experimental design with 3 variables and 2 levels was used. The studied formulation variables were: the percent of polymers, the type of hydroxypropyl-methylcellulose and the ratio between the polymers in the tablet. From the obtained results it was concluded that the most important variable on the release of felodipine was the percent of polymers in the tablet. From the experimental data, an optimal formulation was developed, which has proved to be similar with the dissolution profile of the chosen reference product.

- **Deepa karthikeyan. M, et al.,(2008)[27],**In this study, different grades of hydroxyl propyl methyl cellulose (HPMC) were used to develop floating microspheres of Cefpodoxime Proxetil in order to demonstrate the effect of different viscosities on drug release profile. The Cefpodoxime Proxetil microspheres were prepared by non aqueous solvent evaporation method using different grades of HPMC such as HPMC K15M( 15cps), HPMCK4M(4000cps),HPMC100LV(100cps) and ethyl cellulose. The prepared microspheres were characterized by polymer compatibility (FTIR Scan), percentage yield, Buoyancy percentage, Drug Entrapment Efficiency (DEE) and Invitro drug release was performed by USP Apparatus type I .The better drug release profile was found to be with formulation (FA2 ) with drug: polymer ratio of 1:2, HPMC 15cps showed much significant increase in the drug release while comparing with the other two grades of HPMC.

- **Katayoun.,et al,(2008)[28],**Compared a self-modeling curve resolution method was applied to study the photodegradation kinetics of nitrendipine and felodipine by spectrophotometric method.It is reported that Dihydropyridine are highly photosensitive and converted in the presence of light to compounds that are inactive.

- **Porcellati,C.,et al,(2005)[29],**To assess the duration of the antihypertensive effect of the dihydropyridine calcium antagonist felodipine in conventional and slow release formulations.12 patients with essential hypertension underwent ambulatory blood pressure monitoring at the end of a treatment period with C-F 5mg,E-R 10mg once daily(o.d.) and placebo.C-F,ER-F, and placebo were given in a double-blind 3×3 latin square design 4 times replicated. There was no systematic change in the ABP profile over the three study periods regardless of the treatment. In comparision to placebo, the mean 24hrs systolic and diastolic blood pressures showed a significant and similar reduction after both formulations.

- **Kimy, B.K.,et al,(2005)[30],** prepared Microspheres containing the anti-hypertension drug, felodipine, by the emulsion solvent evaporation method(o/o) using acrylate methacrylate copolymers,Eudragit RL PO and Eudragit RS PO, as wall materials. In order to increase the encapsulation efficiency, a mixed solvent system comprising 1:1 proportions of acetonitrile and dichloromethane was used as a dispersed phase. The release rate of the Eudragit RS PO microspheres was much lower than that of Eudragit RL PO microspheres. Whereas Eudragit RL PO microspheres followed the Higuchi rule, Eudragit RS PO microspheres exhibited a triphasic release profile. It is concluded that drug release rate can be choice of polymer type.

- **Yang.,et al,(2004)[31],** developed a process for producing an oral sustained-release pharmaceutical composition of felodipine is discussed. The process includes mixing together felodipine with an

ionic surfactant, hydrophilic polymer and a release-controlling excipient.The pharmaceutical composition of felodipine produced by the process enhanced the dissolution rate of insoluble drug of felodipine with simultaneously producing pharmaceutical composition of felodipine sustained release with superior bioavailability.

- **Pannarale.,et al,(2003)[32],** Assesed the 24-hr antihypertensive efficacy of an extended release 10mg formulation of the dihydropyridine felodipine for the treatment of mild-moderate essential hypertension.

# 3. Aim and Objective

Hypertension is a major risk for Cardiovascular and stroke complications. The good permeability and the poor water solubility (BCS class II) as well as short biological half-life characteristics of Felodipine selected as a drug candidate for extended release preparations consist 10mg per day tablet preparation. Felodipine belongs to dihydropyridine derivative, which acts as a calcium channel blocker, used as an anti-hypertensive drug.

The aim of the present investigation to develop a once-daily extended release dosage form of felodipine in tablet form using different polymer grade in varying proportions on to determine which concentration best fit to the desired drug profile as per USP.

The core and coated tablet to be evaluated, with respect to the physical and chemical parameters like hardness, thickness, weight variation, friability, assay including *Invitro* drug release study. The optimized batch to be compared with kinetics of drug release, marketed product and similarity, differential factor.

# 4. Plan of Work

- Preformulation studies
  - Drug Excipient interaction study
  - Bulk density
  - Tapped density
  - Compressibility index
  - Hausner's ratio
- Formulation of Felodipine Extended Release tablet by Dry granulation technique.
- Evaluation of compressed tablet
  - Hardness
  - Thickness
  - Weight variation
  - Friability
  - Drug content
  - *Invitro* dissolution study
- Selection of optimized formula based on *Invitro* dissolution profile, and film coating of optimized formula.
- Evaluation of film coated tablet.
  - Average weight
  - Hardness
  - Thickness

- Drug content
- *Invitro* dissolution study

- Comparision of optimized formula with marketed product.
- Release Kinetics.
- Stability studies of best formulation.

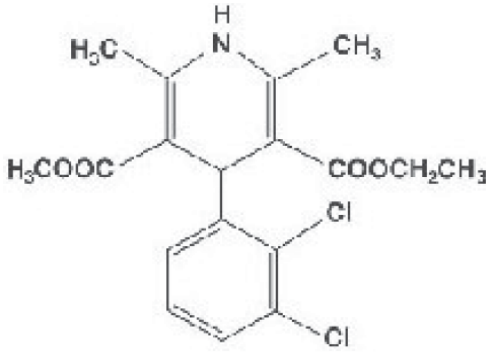
# 5. Drug Profile

## *5*.1 Felodipine: [33-34]

**Category:**

Antihypertensive (Calcium channel blockers)

**Structure:**




**Origin of the substance:**

Felodipine is a dihydropyridine derivative.

**Chemical name:**

Ethylmethyl4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethl3,5pyridinedicarboxylate.

**Molecular formula:** $C_{18}H_{19}C_{12}NO_4$

**Molecular weight :** 384.26

**Description :** Felodipine is a slightly yellowish, crystalline powder. Felodipine is a racemic mixture.

**Solubility :** It is insoluble in water and is freely soluble in dichloromethane and ethanol.

**Melting point :** 142-145˚C

**Pharmacodynamic effects:**

- Felodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing peripheral vascular resistance.

- It can be used as monotheraphy or in combination with other antihypertensive agents, e.g. β-adrenoceptor blockers, diuretics or ACE-inhibitors, in order to achieve an increased antihypertensive effect.

- Felodipine has anti-anginal and anti-ischaemic effects due to improved myocardial oxygen supply/demand balance.

**Mechanism of action:**

- Felodipine is a member of the dihydropyridine class of calcium channel antagonists (calcium channel blockers).

- Felodipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through voltage-gated L-type calcium channels.

- It reversibly competes with nitrendipine and/or other calcium channel blockers for dihydropyridine binding sites, blocks voltage-dependent $Ca^{++}$currents in vascular smooth muscle and blocks potassium-induced contracture.

- Felodipine inhibits electrical and contractile activity of vascular smooth muscle cells via an effect on the calcium channels in the cell membrane and results in vasodilation. The vasodilatory effects of felodipine result in an overall decrease in blood pressure. Felodipine may be used to treat mild to moderate essential hypertension.

**Pharmacokinetics:**

**Absorption and Distribution:**

Following oral administration, felodipine is almost completely absorbed in the gastro intestinal tract and undergoes extensive first-pass metabolism. The absorption Phase is prolonged.

Systemic availability : 20%.

Plasma protein binding : 99%.

Volume of distribution : 10 L/Kg

Biological Half Life : 14 hrs

$T_{max}$ : 2.5 to 5 h.

Both peak plasma concentration and the area under the plasma concentration time curve (AUC) increase liner with doses up to 20 mg.

**Metabolism and Elimination:**

Felodipine is extensively metabolized in the liver by cytochrome P450 3A4 (CYP3A4) and all identified metabolites are inactive. Extensive first pass metabolism.

About 70% of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0.5% of a dose is recovered unchanged in the urine.

**Uses:**

Hypertension

Angina pectoris

Felodipine extended-release tablets may be used alone or concomitantly with other antihypertensive agents.

**Therapeutic Dosage :** 2.5mg, 5mg, 10mg.

**Posology and method of administration:**

The tablets should be swallowed with water and must not be divided, crushed, or chewed. The tablets can be administered without food or following a light meal not rich in fat or carbohydrate.

**Table 4: Brand names& Manufactures**

| Brand Names | Manufactures |
|---|---|
| Plendil | Astrazeneca Pharma Limited |
| Felodipine Extended release tablet | Glenmark generics limited |
| Felo ER | Mylan Pharmaceuticals |
| Felogard | Cipla Limited |
| Felodipine Extended release tablet | Qualitest Pharmaceuticals |

**Overdose:**

Over dosage may cause excessive peripheral vasodilatation with marked hypotension and sometimes bradycardia.

**Contraindication:**

Pregnancy

Uncompensated heart failure

Acute myocardial infarction

Unstable angina pectoris

**Drug Interactions:**

**Anticonvulsants (eg, barbiturates, carbamazepine, hydantoins)**

Felodipine plasma concentrations may be reduced in epileptic patients, decreasing the therapeutic effects. Alternative therapy should be considered.

**Beta-blockers (eg, metoprolol)**

Metoprolol plasma levels may be increased.

**CYP3A4 inhibitors (eg, cimetidine, erythromycin, grapefruit juice, itraconazole, ketoconazole)**

Because of an increase in felodipine bioavailability or decrease in metabolism, felodipine plasma levels may be elevated several-fold, increasing the pharmacologic and adverse effects.

**Histamine $H_2$ antagonists (eg, cimetidine)**

Felodipine plasma levels may be elevated, increasing the pharmacologic and adverse effects.

**Food Interactions:**

Grapefruit juice results in increased peak plasma levels and bioavailability possibly due to an interaction with flavonoids in the fruit juice.

**Adverse Reactions:**

**Cardiovascular** **:** Palpitation (at least 1.5%).

**CNS** **:** Asthenia, dizziness, headache.

**Dermatologic** **:** Flushing, rash.

**EENT** **:** Rhinorrhea, sneezing.

**GI** **:** Constipation, dyspepsia, nausea.

**Respiratory** **:** Cough, upper respiratory infection.

**Packing and Storage:**

Store below 30°C (86°F) .Keep container tightly closed. Protect from light.

## Stability:

Felodipine is stable under ordinary conditions.

## Excipient Profile

### 5.2 Spay Dried Lactose:[35]

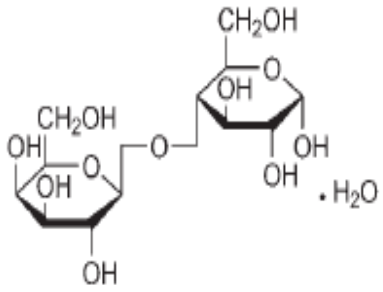
**Nonproprietary Name:**

None adopted.

**Synonyms:**

Flow Lac 100; Lacto press Spray-Dried; NF Lactose–316 FastFlo; NF Lactose–315; Pharmatose DCL 11; Pharmatose DCL 14;Super-Tab Spray-Dried.

**Structural formula:**



**Chemical Name and CAS Registry Number:**

It is a mixture of amorphous lactose, which is a 1:1 mixture of a-and-b-lactose, and O-b-D-galactopyranosyl-(1!4)-a-glucopyranose monohydrate.

**Empirical Formula and Molecular Weight:**

$C_{12}H_{22}O_{11}$ 342.30 (for amorphous)

$C_{12}H_{22}O_{11}\_H_2O$ 360.31 (for monohydrate)

**Description:**

Lactose occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting. Spray-dried direct-compression grades of lactose are generally composed of 80–90% specially prepared pure a-lactose monohydrate along with 10–20% of amorphous lactose.

**Functional Category:**

Binding agent; directly compressible tablet excipient; tablet and capsule diluents; tablet and capsule filler.

**Stability and Storage Conditions:**

Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

**Incompatabilities:**

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, amfetamines and lisinopril.

**Applications:**

Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as spray-dried lactose and anhydrous lactose.

## 5.3 Hydroxy Propyl Methyl Cellulose:[36]

**Nonproprietarty names:**

BP : Hypromellose

JP : Hydroxypropyl methyl cellulose

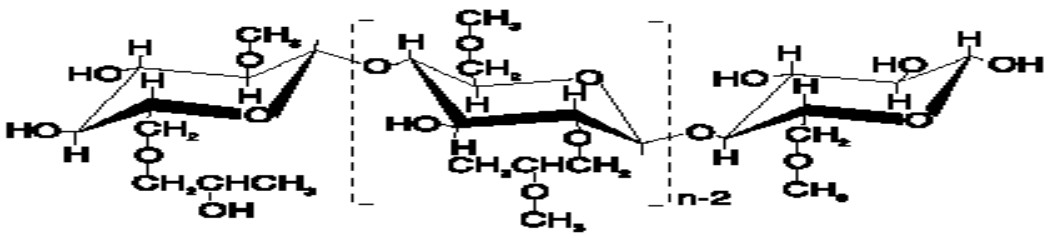
Ph.Eur : Hypromellosum

USP : Hypromellose

**Synonyms:**

Benecel MHPC; E464; hydroxypropyl methyl cellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxyl propylcellulose; Metolose.

**Structural formula:**




**Structure of HPMC**

**Chemical name:** Cellulose hydroxypropyl methyl ether.

**Functional category:**

Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, tablet binder, viscosity increasing agent.

**Applications in Pharmaceutical Formulation or Technology:**

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations.

- Concentrations between 2% and 5% w/w may be used as a binder in either wet-or dry-granulation processes.

- High-viscosity grades may be used to retard the release of drugs from the levels of 10-80%w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20%w/w are used for film-forming solutions to film-coat tablets.

- Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. It is also used as a suspending and thickening agent in topical formulation.

- Hypromellose at concentrations between 0.45-1.0%w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

**Description :** HPMC is an odorless and tasteless, white or creamy-white fibrous or granular powder.

**Melting point :** Browns at 190–200°C; chars at 225–230°C.Glass transition temperature is 170–180°C.

**Solubility:**

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixture of methanol and dichloromethane, and mixtures of water and alcohol.

**Viscosity (dynamic):**

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared; Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of their required amount of water. The water should be vigorously stirred and heated to 80–90°C and then the remaining hypromellose should be added. Then sufficient cold water should be added to produce the required volume.

**Table 5: Viscosity ranges of HPMC**

| Methocel product | USP 28 designation | Nominal viscosity (mPa s) |
|---|---|---|
| *Methocel K100 Premium LVEP* | 2208 | 100 |
| *Methocel K4M Premium* | 2208 | 4000 |
| *Methocel K15M Premium* | 2208 | 15 000 |
| *Methocel K100M Premium* | 2208 | 100 000 |
| *Methocel E4M Premium* | 2910 | 4000 |
| *Methocel F50 Premium* | 2906 | 50 |
| *Methocel E10M Premium CR* | 2906 | 10 000 |
| *Methocel E3 Premium LV* | 2906 | 3 |
| *Methocel E5 Premium LV* | 2906 | 5 |
| *Methocel E6 Premium LV* | 2906 | 6 |
| *Methocel E15 Premium LV* | 2906 | 15 |
| *Methocel E50 Premium LV* | 2906 | 50 |
| *Metolose 60SH* | 2910 | 50, 4000, 10 000 |
| *Metolose 65SH* | 2906 | 50, 400, 1500, 4000 |
| *Metolose 90SH* | 2208 | 100, 400, 4000, 15 000 |

**Stability and storage:**

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11.Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

**Incompatibilities:**

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts to form insoluble precipitates.

## 5.4 Micro Crystalline Cellulose:[37]

**Nonproprietary Name:**

BP : Microcrystalline cellulose

JP : Microcrystalline cellulose

PhEur : Cellulosum microcristallinum

USP : Microcrystalline cellulose

**Synonyms:**

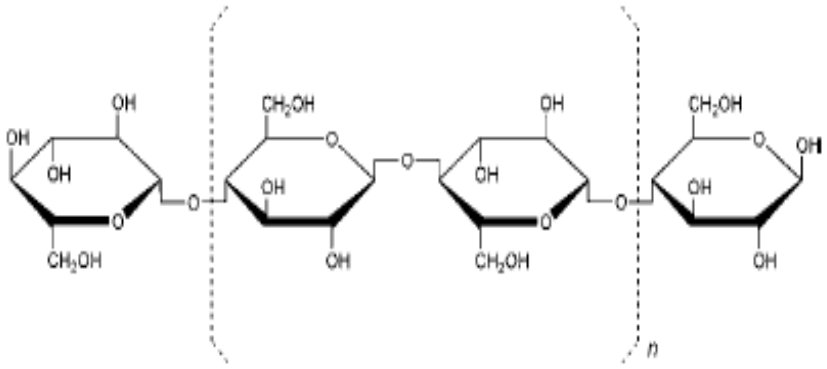
Avicel PH; Celex; cellulose gel; Celphere; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; abulose; Vivapur.

**Chemical Name and CAS Registry Number:** Cellulose [9004-34-6]

**Empirical Formula:** $(C_6H_{10}O_5)_{\mathbf{n}}$ where n = 220.

**Molecular weight :** 36000

**Structural formula:**



**Functional**

Adsorbent, suspending agent; tablet and capsule diluent; tablet disintegrant.

**Applications:**

Microcrystalline cellulose is primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet- granulation and direct-compression processes. In addition to its used as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tabletting. Microcrystalline cellulose is also used in cosmetics and food product.

**Description:**

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

**Typical Properties**

Bulk density : 0.337g/$cm^3$

0.32g/$cm^3$Avicel pH-101

Density (tapped) : 0.478g/$cm^3$;

0.45g/$cm^3$ for Avicel pH-101

Density (true) : 1.512–1.668 g/$cm^3$

Flowability : 1.41g/s for Emcocel 90M (9)

**Moisture content:**

Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

**Stability and Storage Conditions:**

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

**Incompatibilities:**

Microcrystalline cellulose is incompatible with strong oxidizing agents.

## 5.5 Talc:[38]

**Nonproprietary Names:**

BP : Purified talc

JP : Talc

PhEur : Talc

USP : Talc

**Synonyms:**

Altalc;Hydrous magnesium calcium silicate; Hydrous magnesium silicate; Magsil star; Powdered talc; Purified French talc; Purtalc; Soapstone.

**Chemical Name :** Talc

**Empirical Formula :** $Mg_6 (Si_2O_5)4(OH)_4$

**Functional Category:**

Anticaking agent; Glidant; Tablet and capsule diluents; Tablet and capsule lubricant.

**Description:**

Talc is a very fine, white-greyish, odorless, impalpable, crystalline powder.

**Moisture Content:**

Talc absorbs insignificant amount of water at 258˚C and relative humidities upto about 90%.

**Storage Conditions:**

Talc should be stored in a well-closed container in a cool, dry place.

**Incompatibilities:**

Incompatible with quaternary ammonium compounds.

**Applications:**

Talc was widely used in oral solid dosage formulations as a lubricant and diluents. It was also used as a lubricant in tablet formulations in a novel powder coating for extended release pellets and as an absorbant.

## 5.6 Sodium Stearyl Fumarate:[39]

**Nonproprietary Names:**

BP : Sodium stearyl fumarate

PhEur : Natrii stearylis fumaras

USPNF : Sodium stearyl fumarate

**Synonyms:**

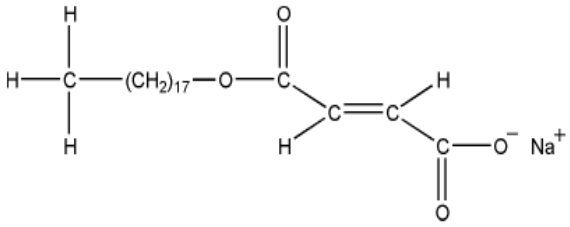
Fumaric acid, octadecyl ester, sodium salt; sodium monostearyl fumarate

**Chemical Name and CAS Registry Number:**

2-Butenedioic acid, mono octadecyl ester, sodium salt [4070-80-8]

**Empirical Formula and Molecular Weight :** $C_{22}H_{39}NaO_4$, 390.5

**Structural formula:**



**Functional Category:** Tablet and capsule lubricant.

**Applications in Pharmaceutical Formulation or Technology:**

It is used as a lubrication capsule and tablet formulations at 0.5–2.0% w/w concentration. It is also used in certain food applications.

**Description:**

Sodium stearyl fumarate is a fine, white powder with agglomerate so flat, circular-shaped particles.

**Stability and Storage condition:**

At ambient temperature, sodium stearyl fumarate is stable for upto 3years when stored in amber glass bottles with polyethylene screw caps. The bulk material should be stored in a well-closed container in a cool, dry place.

**Incompatibilities:**

Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.

## 5.7 Isopropyl Alcohol:

**Nonproprietary Names**

Isopropyl Alcohol (BP, JP, PhEur, USP)

**Synonyms:**

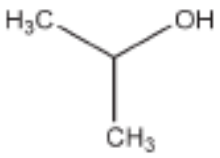
Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol, 2-propanol, sec-propyl.

**Chemical Name** **:** Propan-2-ol

**Empirical Formula** **:** $C_3H_8O$

**Molecular Weight** **:** 60.1

**Structural Formula** **:**




**Description:**

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor and it has a slightly bitter taste.

**Typical Properties:**

| | | |
|---|---|---|
| **Boiling point** | **:** | $82.4^0$C |
| **Flammability** | **:** | Flammable**.** |
| **Viscosity (dynamic)** | **:** | 2.43mPasat$20^0$C |
| **Specific gravity** | **:** | 0.786 |

**Functional Category:**

Disinfectant, solvent.

**Solubility:**

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.

**Applications in Pharmaceutical Formulation or Technology:**

Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

**Storage Conditions**

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

**Incompatibilities**

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

**Safety:**

Isopropyl alcohol is most frequently used in topical pharmaceutical formulations where it may act as a local irritant. When applied to the eye it can cause corneal burns and eye damage.

**5.8 Methylene Chloride :**

**Chemical Name :** Dichloromethane

**Other Names :** Methylene chloride, methlene dichloride, narkotil, solaesthin.

**Appearance :** Colourless liquid

**Melting point :** -96.7˚C

**Taste :** Sweet aroma

**Applications:**

DCM's volatility and ability to dissolve a wide range of organic compounds makes it a useful solvent for many chemical processes. Concerns about its health effects have led to a search for alternatives in many of these applications.

- Paint stripping
- Pharmaceutical manufacturing
- Metal cleaning
- Paint remover

# 6. Materials and Methods

**Table 6: Materials used in the study**

| S.No | Materials | Source |
|---|---|---|
| 1. | Felodipine | Polydrug Lab Pvt Ltd, Bangalore. |
| 2. | Lactose DCL 11 | DMV ,Holland |
| 3. | Hydroxy propyl Methyl Cellulose K100 | Rolex Chemical Industries, Mumbai. |
| 4. | Hydroxy propyl Methyl Cellulose K4M | S.D.Fine Chem.Ltd., Mumbai. |
| 5. | Microcrystalline Cellulose pH 102 | Ankit pulps chemicals pvt. |
| 6. | Talc | S.D.Fine Chemicals Ltd, Mumbai. |
| 7. | Sodium Stearyl fumarate | S.D.Fine Chemical Ltd, Mumbai. |
| 8. | Instacoat | Dow Chemicals, Canada. |
| 9. | Methylene Chloride | Lee Changyung Chemicals. |
| 10. | Isopropyl alcohol | Lee Changyung Chemicals. |

**Table 7: Equipments used in the study**

| Sl. No | Equipments | Manufacturers/ Suppliers |
|---|---|---|
| 1 | Digital Weighing balance | Essae,Banglore |
| 2 | Vernier caliper (digital) | Mitutoyo corps, japan |
| 3 | Digital hardness tester | Remi |
| 4 | Friability apparatus,ET-2 | Electrolab, Mumbai |
| 5 | Tap density apparatus,ETD-1020 | Electrolab,Mumbai |
| 6 | PH meter | Thermolab,Mumbai |
| 7 | Double cone blender | Vamp, Mumbai |
| 8 | Rotary Tablet compression machine, CMP210 | Elit pilot press |
| 9 | Dissolution test apparatus,TDT-08L | Electrolab,India |
| 10 | UV-Spectrometer,UV-1601 | Shimadzu, Japan |
| 11 | HPLC | Waters HPLC, India |
| 12 | Photostability and humidity chamber | Thermolabs, Mumbai. |

# Experimental Methods

## *6.1 Preformulation Studies:*

Preformulation studies can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipient. Preformulation investigations are designed to identify those physiochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. It is the first step in the rational development of dosage forms.

### 6.1.1 Preparation of standard calibration curve of felodipine:

100mg of felodipine was accurately weighed and dissolved in 25 ml of methanol in 100ml volumetric flask and make up the volume using methanol, to make (1000 µg/ml) standard stock solution (I). Then 1ml stock solution (I) was taken in another 100ml volumetric flask and further dilute in 100ml of methanol to make (10µg/ml) standard stock solution (II), then final concentrations were prepared 2,4,6,8, and 10 µg/ml with0.1N HCL.The absorbance of standard solution was determined using UV/VIS spectrophotometer at 241nm and values were shown in table and **Fig.6**

### 6.1.2 Drug- Excipient Interaction Studies:[40]

The compatibility of drug and excipient is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipient under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

**FT-IR Analysis:**

Potassium Bromide Pellet (KBr) method was used in the study. Test samples were prepared by physical mixing of felodipine and exicipients in ratios of 1:1. Initially 100mg of Potassium Bromide powder was mixed with 2mg of each

sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBr pellet was placed in sample holder of Bruker FT-IR spectrophotometer. The spectra were recorded in the wave number region of 2000-500cm-$^{1}$. In each case the spectra was compared with the pure felodipine spectrum to detect the interactions between drug and excipient.

The FTIR Graphs of drug and excipients were shown in the **Fig.7**

### *6.1*.3 Physical properties:[41]

For a drug substance to formulate into a dosage form, it is necessary to study the physiochemical properties of bulk drug.

**Determination of bulk density and tapped density:**

#### 6.1.3.1 Bulk density:

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies (M).It is expressed in gm/ml. Weighed quantity of powder was transferred into a 50 ml measuring cylinder without tapping, during transfer the volume occupied by granules was measured ($V_{0)}$. Bulk density was measured by using formula**.**

**Bulk density = $M/V_o$**

**Where,**

**M = Mass of the powder**

**$V_o$= Volume of the powder**

#### 6.1.3.2 Tapped Density:

Weighed quantity of powder was taken into graduated cylinder, volume occupied was noted down (M). Then cylinder was subjected to 500 taps in tapped

density tester (Electro Lab USP II), the final reading was denoted by ($V_i$).The % Volume variation was calculated by using the following formula.

**Tapped density = $M/V_i$**

**Where,**

**M = Mass of the powder**

**$V_i$ = Tapped volume**

### 6.1.3.3 Carr's index:

Compressibility is the ability of powder to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of powder were determined, which is given as Carr's compressibility index.

**$CI=V_i-V_0 / V_i \times 100$**

**Where,**

**CI = Compressibility index**

**$V_0$ = Bulk density**

**$V_i$ = Tapped density**

**Table 8: Compressibility index**

| Compressibility index (%) | Flow characters |
|---|---|
| < 10 | Excellent |
| 11-15 | Good |
| 16-20 | Fair |
| 21-25 | Passable |
| 26-31 | Poor |
| > 32 | Very poor |

### 6.1.3.4 Hausner's ratio:

It is a measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

**Hausner Ratio = $V_i$ / Vo**

**Where,**

**$V_0$ = Bulk density**

**$V_i$ = Tapped density**

**Table 9: Hausner ratio**

| Flow characters | Hausner ratio |
|---|---|
| Excellent | 1.11 |
| Good | 1.12 – 1.18 |
| Fair | 1.19 – 1.25 |
| Passable | 1.26 – 1.34 |
| Poor | 1.35 – 1.45 |
| Very poor | 1.46 – 1.59 |
| Very Very poor | >1.60 |

### 6.1.4.5 Angle of repose:

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure the flow ability of powder.

**Procedure:**

A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface .The radius was measured and angle of repose was calculated by using the formula.

$$\theta = \tan^{-1}(h/r)$$

**Where,**

**θ = Angle of repose,**

**h = height of the heap of pile,**

**r = radius of base of pile.**

**Table 10: Flow Properties and Corresponding Angle of Repose**

| Flow properties | Angle of repose(θ) |
|---|---|
| Excellent | 25-30 |
| Good | 31-35 |
| Fair – aid | 36-40 |
| Passable | 41-45 |
| Poor | 46-55 |
| Very poor | 56-65 |
| Very very poor | >66 |

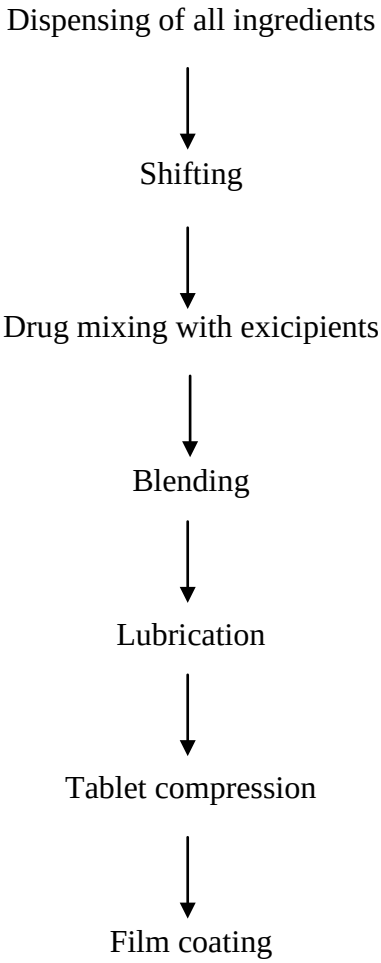
## 6.2 Formulation Development

The main objective of this formulation development is to design a extended release drug delivery system in the form of a tablet.

**Dry granulation method:**

Felodipine extended release tablet were prepared by dry granulation method.

**Fig 5: Manufacturing flow chart**



**Procedure:**

**Step 1: Weighing**

- All the ingredients were weighed accurately as per manufacturing formula (Table 10).

**Step 2: Shifting**

- Accurately weighed quantity of Felodipine was sifted through 30 # mesh. Weighed quantity of Lactose DCL11, MCC 102, HPMC K100, HPMC K4M was passed through 30# mesh separately.

**Step 3: Mixing**

- Felodipine was mixed with Lactose DCL11 by geometrical mixing. HPMC K100 and HPMC K4 M was mixed with MCC pH102 by geometrical mixing.

**Step 4: Shifted**

- Talc was passed through 60# mesh. Sodium stearyl fumarate was passed through 60# mesh.

**Step 5: Blending**

- Finally, load step3 blend into double cone blender and mixed thoroughly for 15 minutes.

**Step 6: Compression**

- Blended material was transferred to a tablet machine and compression using 27 stationed compression machine with 14/32 inch (11.11mm), standard concave plain on both sides. Blended material was loaded in a

hopper and powder was compressed to tablets by operating rotary tablet compression machine.

**Core tablet specifications:**

**Description :** White coloured, circular shaped, slightly biconvex, uncoated Extended release tablet.

**Average weight (mg) :** 450± 5%

**Hardness :** Not Less Than 4 kg/ $cm^2$

**Thickness :** 4.10mm to 4.50mm

**Friability :** Not More Than 1.0 %

**Assay of API :** 90%-110%

**Dissolution (as per USP) :**[41]

1st hour - 5-30%

$4^{th}$ hour - 45-70%

$8^{th}$ hour - NLT 80%

**Step 6: Film coating**

- Isopropyl alcohol was transferred into a stainless steel vessel. To this Instacoat was added and stirred well.
- Finally Methylene Chloride was added under constant stirring to avoid lumps formation.
- The dispersion was filtered through mesh #100.
- The prepared tablets were coated in a coating pan till the average weight build up to 3% w/w.

**Table 11: Film coating specifications**

| | |
|---|---|
| **Inlet temperature(˚c)** | 40-50 |
| **Outlet temperature(˚c)** | 40-45 |
| **Spray pump( rpm)** | 6-8 |
| **Air pressure(kg/cm$^2$)** | 4-5 |
| **Pan (rpm)** | 4-8 |

**Coated tablet specifications:**

**Description:** White coloured, circular shaped, slightly biconvex, film coated Extended release tablet

**Average Weight (mg)** **:** 463.5± 5%

**Thickness** **:** 4.20-4.60mm

**Assay of API** **:** 90%-110%

**Dissolution (as per USP) :**[41]

1st hour - 5-30%

4$^{th}$ hour - 45-70%

8$^{th}$ hour - NLT 80%

**Table12: Formulation of Felodipine Extended Release tablet**

| Ingredients | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) | F6 (mg) | F7 (mg) | F8 (mg) | F9 (mg) |
|---|---|---|---|---|---|---|---|---|---|
| **Felodipine** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Lactose DCL11** | 105 | 120 | 220 | 228 | 226 | 230.50 | 246 | 249.20 | 243.20 |
| **HPMC K100** | 77 | 50 | 77 | 50 | 27 | 20.50 | 7 | 12 | 15 |
| **HPMC K4M** | 16 | 12 | 16 | 14 | 14 | 12 | 5 | 7 | 10 |
| **MCC 102** | 67 | 83 | 120 | 141 | 166 | 170 | 175 | 164.80 | 164.80 |
| **Talc** | 2.5 | 2.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| **Sodiumstearyl Fumarate** | 2.5 | 2.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| **Film coating** | | | | | | | | | |
| **Instacoat** | _ | _ | _ | _ | _ | _ | _ | _ | 13.5 |
| **Isopropyl alcohol** | _ | _ | _ | _ | _ | _ | _ | _ | 105 |
| **Methylene chloride** | _ | _ | _ | _ | _ | _ | _ | _ | 178 |
| **Weight gain (%)** | | | | | | | | | 3% |
| **Total weight (mg)** | 280 | 280 | 450 | 450 | 450 | 450 | 450 | 450 | 463.5 |

## 6.3 Evaluation of Core and Film Coated Tablet

***1. General appearance:***

The general appearance of the tablet from each formulation batch was observed.

***2 . Weight variation:***

Twenty tablets were selected randomly from a particular batch and weighed individually and average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviations shown in table and none deviate by more than twice the percentage**.**

**Table 13: Weight variation limits (as per USP)**

| Average weight of tablet(mg) | Maximum% difference allowed |
|---|---|
| 130mg or less | 10 |
| 130-324 | 7.5 |
| 324 or more | 5 |

***3. Thickness:***

Ten tablets from the representative sample were taken and individual tablet thickness was measured by using digital vernier calipers. Average thickness and standard deviation values were calculated.

***4. Hardness:***

Tablet hardness was measured by using Monsanto hardness tester. From each batch ten tablets were measured for the hardness and average values was recorded.

***5. Friability Test:***

From each batch, 10 tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were dedusted and reweighed. The friability was calculated as the percentage weight loss.

% Friability was calculated as follows

**% Friability = $(W_1 – W_2) \times 100/W_1$**

Where, $W_1$ = Initial weight of the tablets.

$W_2$ = Final weight of the tablets.

Friability values below 1 % are generally acceptable.[42]

***6. Assay (as per USP):[43]***

**Buffer solution:**

6.9 g of monobasic sodium phosphate was accurately weighed and dissolved in 800 ml of water using 1000-ml volumetric flask. Adjust with 1 M phosphoric acid to a pH of 3.0 ± 0.05, dilute with water to volume, and mix.

**Mobile phase:**

A filtered and degassed mixture of mobile phase was prepared.

Buffer solution: acetonitrile: methanol (400:400:200).

**Standard stock preparation:**

100mg of felodipine was dissolved in 50ml of methanol using 50ml volumetric flask.

**Standard preparation:**

1ml of standard stock solution was transferred into a 100 ml volumetric flask and diluted upto the volume with mobile phase and mixed.

**Sample preparation:**

Twenty tablets were weighed to obtain the average weight and were powdered by trituration. An accurately weighed portion of the powder, equivalent to 10 mg of active ingredient, was mixed with 40ml of acetonitrile and 20ml of methanol and sonication for 5 minutes. 30ml of Buffer solution was added and shaked by mechanical means for 30 minutes. The solution was allowed to cool at room temperature and diluted with Buffer solution to the volume and mixed.10ml of the supernatant was transferred into a 50ml volumetric flask and diluted with mobile phase to the volume and mixed. The resulting solution was passed through 0.5µ membrane filter.

**Chromatographic system:**

Mode : Liquid chromatograph

Detector : 362-nm detector

Column : 4.6-mm × 15-cm column that contains packing L1.

Flow rate : 1 ml per minute.

Column efficiency : Not less than 1500 theoretical plates

Relative standard deviation for replicate injections is NMT 2.0%.

Injected about 10µl portion of the Standard preparation and the Assay preparation into the chromatograph, recorded the chromatograms, and measured the responses for the major peaks.

The% assay can be calculated by the formula:

$$\frac{\text{Sample Area}}{\text{Standard Area}} \times \frac{\text{Standard weight}}{\text{dilution}} \times \frac{\text{dilution}}{\text{sample weight}} \times \frac{\text{Average weight}}{\text{LC}} \times \frac{P}{100} \times 100$$

***7. Invitro drug release studies:[44]***

**Medium** **:** 1% (w/v) polysorbate 80 in water; 500 ml.

**Apparatus** **:** USP I -Basket

**RPM** **:** 100

**Temperature** **:** 37 ± 0.5˚C

**Sampling Time** **:** 1, 2,4, 6 and 8 hours.

**Buffer solution:**

6.9 g of monobasic sodium phosphate was accurately weighed and dissolved in 400 ml of water using 1000-ml volumetric flask. Add 8.0 ml of 1 M phosphoric acid, diluted with water to volume, and mixed.

**Mobile phase:**

A filtered and degassed mixture of mobile phase was prepared.

Buffer solution: acetonitrile: methanol (400:400:200).

**Standard stock solution:**

Accurately 40mg of Felodipine working standard was weighed and transferred into a 200-ml volumetric flask, add 200 ml of methanol. Sonicate for 2 minutes, cool, diluted with methanol to volume, and mixed.

**Standard working solutions:**

10ml of Standard stock solution was transferred into a 100ml volumetric flask, dilute with medium to volume and mixed.

**Test solution:**

10mg tablet was transferred into a 500 ml medium. A portion of the solution was passed through 0.45-µm filter. Withdrawn amount was replaced with Medium.

**Chromatographic system:**

| | |
|---|---|
| Mode | : Liquid chromatograph |
| Detector | : 254-nm detector |
| Column | : 4.6-mm × 15-cm column that contains packing L1. |
| Flow rate | : 1 ml per minute. |
| Capacity factor (k ¢) | : Not less than 5 |
| Column efficiency (N) | : Not less than 1500 theoretical plates. |
| Tailing factor | : Not more than 1.5. |

Relative standard deviation for replicate injections is not more than 2.0%.

Injected about 20 µl portion of the Standard working solution and the Test solution into the chromatograph, recorded the chromatograms, and measured the peak responses.

**Calculation:**

$$\frac{\text{Sample Area}}{\text{Standard Area}} \times \frac{\text{Standard weight}}{\text{dilution}} \times \frac{\text{volume of medium}}{\text{sample weight}} \times \frac{\text{Average weight}}{\text{LC}} \times 100$$

### *6.4 Release kinetics:* [45-48]

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time
   (first order kinetic model)

2. Cumulative percent drug release versus square root of time
   (Higuchi's model)

3. Cumulative percent drug release versus time
   (zero order kinetic model)

4. Log cumulative Percent Drug released versus log time
   (korsmeyers model)

**Drug release kinetics-model fitting of the dissolution Data**:

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyers-peppas models. Other release parameters, difference factor ($f_1$), similarity factor ($f_2$) can be used to characterize drug dissolution / release profile with the marketed product.

**1. Zero-order kinetics:**

A zero-order release would be predicted by the following equation.

$$Qt = Q_o + K_o t \qquad \text{eq (1)}$$

Where,

Qt = amount of drug dissolved in time t

$Q_o$ = Initial amount of drug in solution

$K_{ot}$ = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to $k_o$.

**2. First-order kinetics:**

A first order release would be predicted by the following equation.

$$\text{Log } C = \text{Log Co} - K_t / 2.303 \qquad \text{eq (2)}$$

Where

C = Amount of drug remained at time t

$C_o$ = Initial concentration of drug

K = First-order rate constant

The data obtained rate plotted as log cumulative percentage of drug remaining versus time which would yield a straight line with a slope of −k/2.303.

**3. Higuchi model:**

Drug release from the matrix devices by diffusion has been described by following higuchi's classical diffusion equation.

$$\mathbf{Q = [DE/ \tau(2A- ECs) C_{st} ]} \qquad \text{eq (3)}$$

Where

Q = Amount of drug release at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

$C_s$ = solubility of the drug in the matrix

E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$$\mathbf{Q = Kt^{½}} \qquad \text{eq (4)}$$

When the data obtained were plotted as cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

**4. Korsmeyers Peppas model:**

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

$$\mathbf{M_t / M_{ά} = Kt^n} \qquad \text{eq (5)}$$

Where,

$M_t / M_{\acute{a}}$ = fraction of drug released at time‘t’

K = Constant incorporating the structural and geometrical Characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$$\textbf{Log } M_t / M_{\acute{a}} = \textbf{Log K+ n Log t} \quad \text{eq (6)}$$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept.

The value of n for a cylinder is <0.45 for fickian release, > 0.45 and < 0.89 for non-fickian release, 0.89 for the case 2 type release and > 0.89 super case 2 type release.

### *6.4 Similarity Factor and Differential Factor Calculation:*

The similarity factor ($f_2$) was defined by CDER, FDA, and EMEA as the “logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and marketed release profiles”. Dissimilarity or difference factor ($f_1$) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and marketed release profiles are identical and increases proportionally with the dissimilarity between the two profiles. There are several methods for dissolution profile comparison. $f_2$ is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors $f_1$& $f_2$.

$$f_1 = \{ [ \sum_{t=1}^{n} | R_t - T_t | ] / [ \sum_{t=1}^{n} R_t ] \} . 100 \quad \text{eq (1)}$$

$$f_2 = 50. \text{Log} \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2 ]^{-0.5} . 100\} \quad \text{eq (2)}$$

Where '$R_t$' and '$T_t$' are the cumulative percentage dissolved at each of the selected n time point of the marketed & test product respectively. The factor $f_1$ is proportional to the average difference between the two profiles, where as factor $f_2$ is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor $f_2$ and its significance is shown in the following

**Table 14: Similarity factor f2 and its significance**

| S. No. | Similarity factor (f2) | Significance |
|---|---|---|
| 1. | <50 | Test and Ditropan profiles are dissimilar. |
| 2. | 50 -100 | Test and Ditropan profiles are similar. |
| 3. | 100 | Test and Ditropan profiles are identical. |
| 4. | >100 | The equation yields a negative value. |

### *6.5 Stability Studies:*[49-51]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The selected batches were charged on accelerated stability as per ICH guidelines.

**Stability studies of selected formulations:**

Stability studies were conducted for the formulation F-9 .The storage conditions used for stability studies were Accelerated condition (40°C±2°C/75%±5%RH).Sample of tablets were analyzed after 1, 2 and 3 months for physical characters and assay were performed followed by *in vitro* dissolution.

# 7. Results and Discussion

## *7.1 Calibration Curve:*

**Table 15: Calibration curve of felodipine**

| S.No | Concentration(µg/ml) | Absorbance(nm) |
|---|---|---|
| 1 | 2 | 0.126 |
| 2 | 4 | 0.258 |
| 3 | 6 | 0.385 |
| 4 | 8 | 0.508 |
| 5 | 10 | 0.618 |

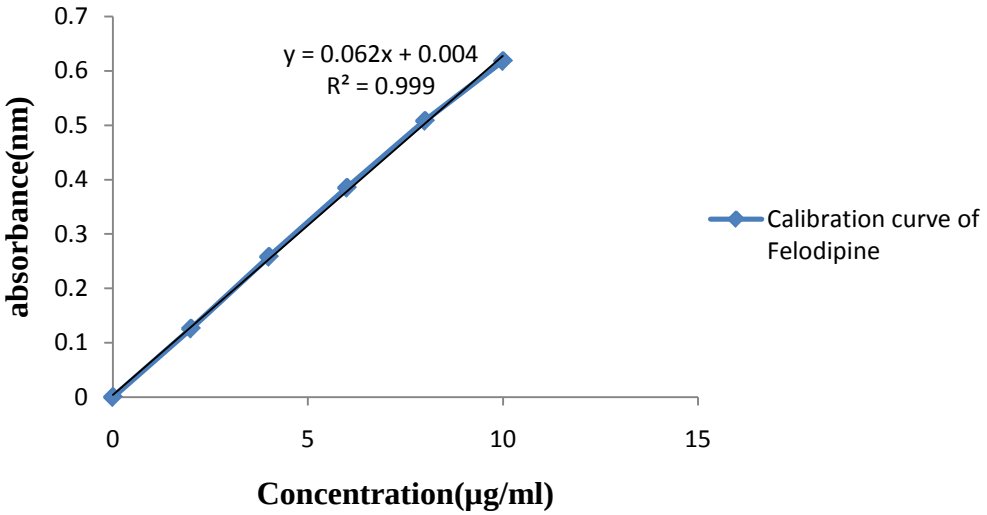



**Figure 6: Calibration curve of felodipine**

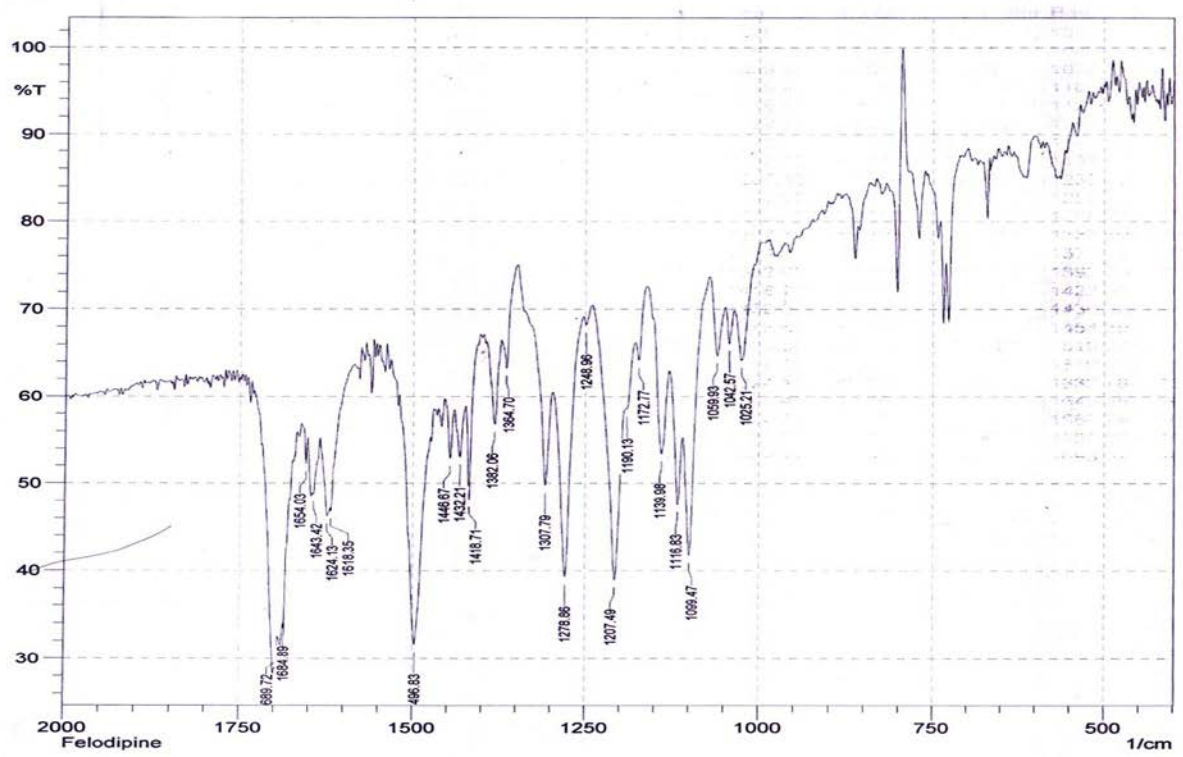



**Fig 7: FT-IR Spectrum of Felodipine**

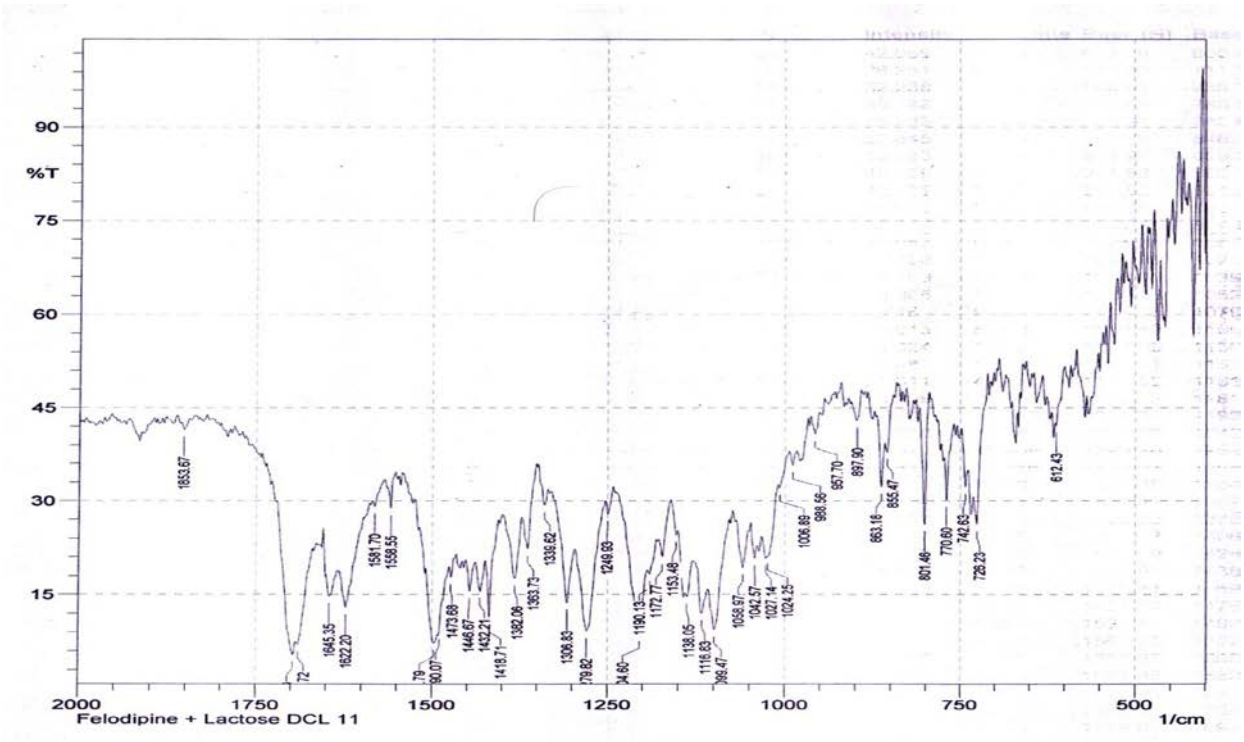



**Fig 8 : FT-IR Spectrum of Felodipine + Lactose DCL 11**

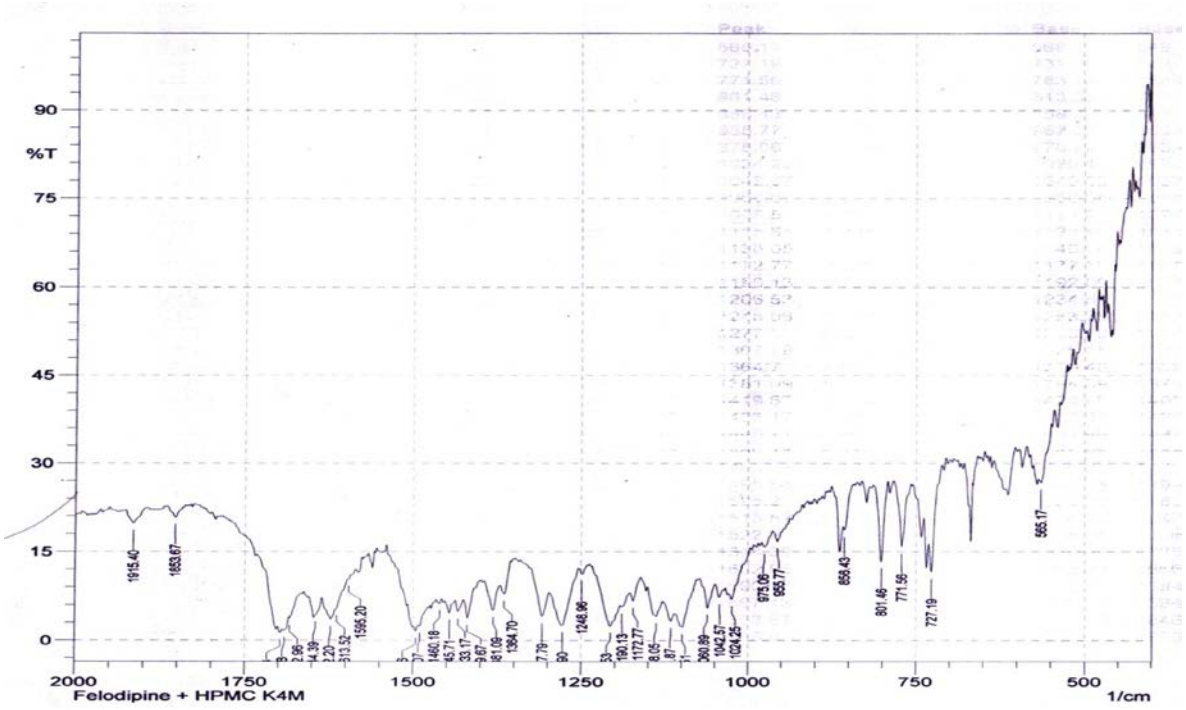



**Fig 9: FT-IR Spectrum of Felodipine+ HPMC K4M**

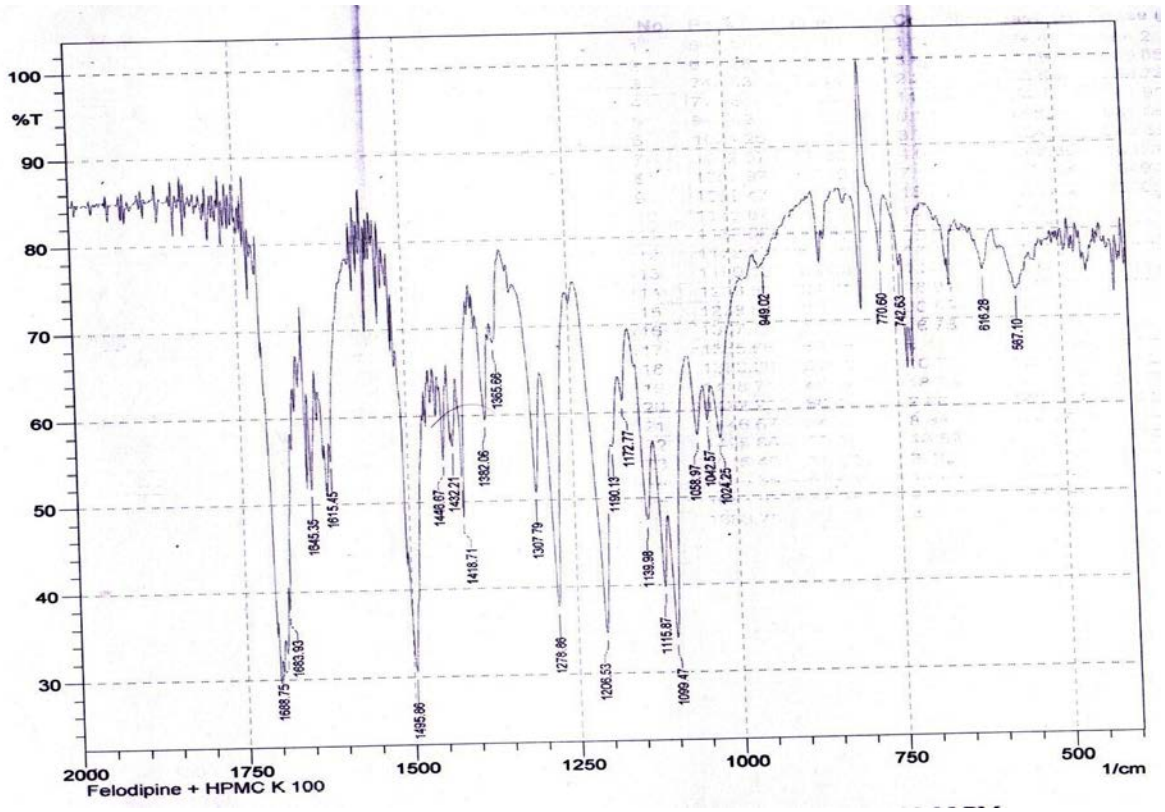



**Fig 10: FT-IR Spectrum of Felodipine+ HPMC K100**

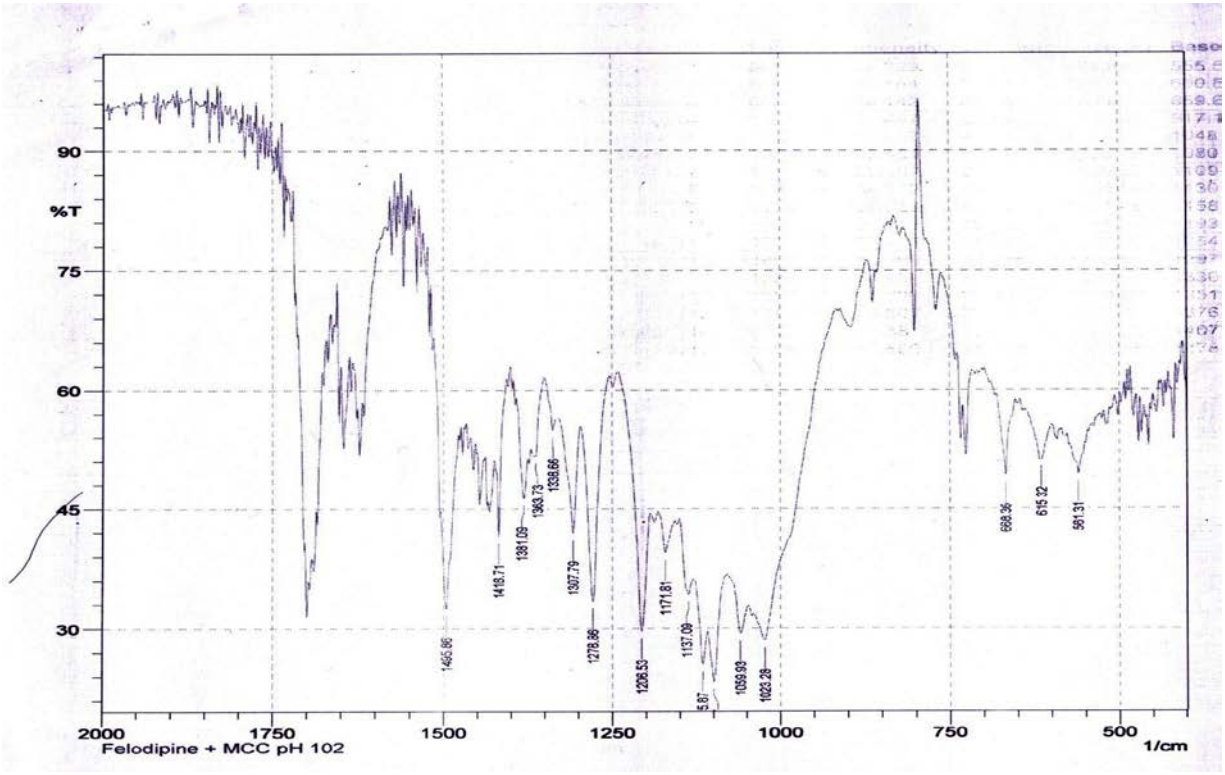



**Fig 10: FT- IR Spectrum of Felodipine+ MCC pH 102**

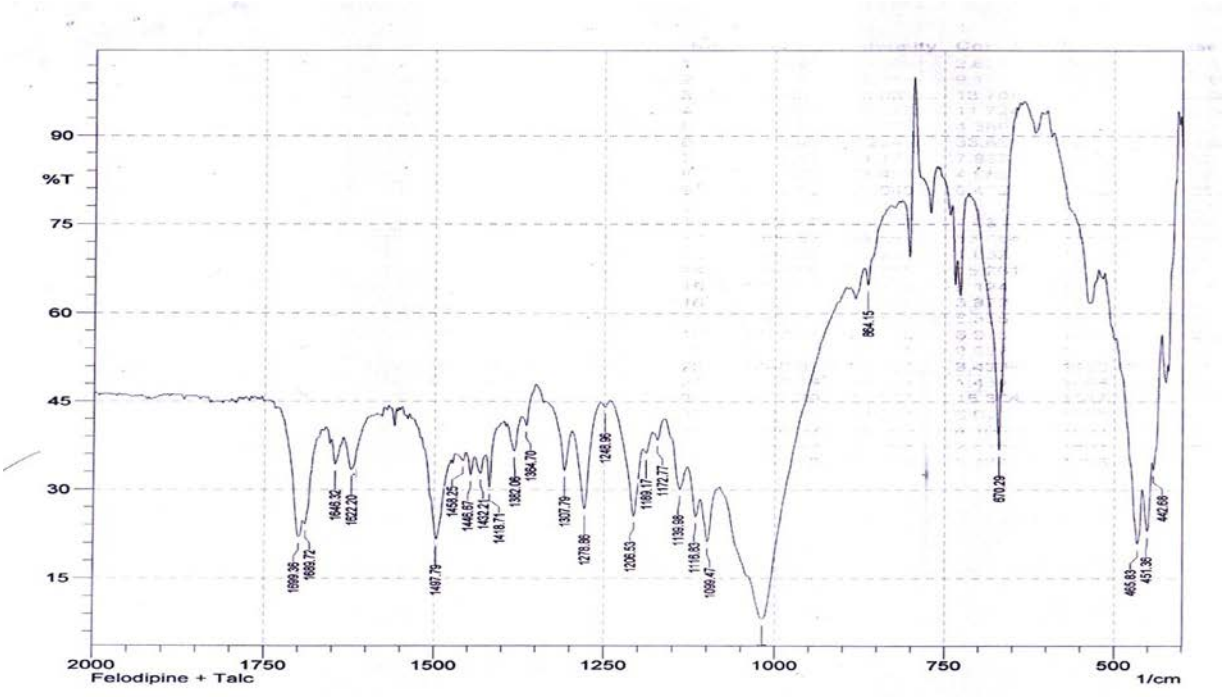



**Fig 11: FT- IR Spectrum of Felodipine + Talc**

## 7.2 *Evaluation of granules:*

**Table 16: Evaluation of granules**

| Formulation | Bulk density (g/ml)±SD | Tapped density (g/ml) ±SD | Hausner's Ratio ±SD | Carr's index ±SD | Angle of repose(θ) ±SD |
|---|---|---|---|---|---|
| **F1** | 0.238±0.02 | 0.312±0.02 | 1.41±0.01 | 29.7±0.49 | 62.8±0.18 |
| **F2** | 0.260±0.01 | 0.358±0.01 | 1.38±0.14 | 27.2±0.87 | 58.3±0.36 |
| **F3** | 0.432±0.04 | 0.524±0.04 | 1.22±0.02 | 18.1±0.13 | 31.6±0.28 |
| **F4** | 0.427±0.03 | 0.516±0.04 | 1.21±0.03 | 17.2±0.20 | 30.2±0.22 |
| **F5** | 0.420±0.03 | 0.510±0.03 | 1.20±0.04 | 17.6±0.10 | 29.9±0.16 |
| **F6** | 0.425±0.04 | 0.514±0.03 | 1.21±0.03 | 17.3±0.22 | 27.4±0.44 |
| **F7** | 0.436±0.05 | 0.523±0.04 | 1.19±0.05 | 16.6±0.30 | 26.5±0.59 |
| **F8** | 0.438±0.05 | 0.525±0.05 | 1.18±0.05 | 16.5±0.30 | 27.5±0.46 |
| **F9** | 0.455±0.06 | 0.531±0.05 | 1.16±0.06 | 14.2±0.56 | 25.1±0.41 |

**Mean±SD(n=3)**

The results show that all the formulation blends showed good flow properties and can form uniform tablets, except F1, F2.

### *7.3 Evaluation of Core tablet:*

**Table 17: Evaluation of Core tablet**

| Formulations | Weight Variation (mg) | Hardness ($kg/cm^{2)}$ | Thickness (mm) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| **F3** | 454±0.42 | 9.0±0.06 | 4.40±0.05 | 0.08±0.04 | 98.64±0.07 |
| **F4** | 449±0.28 | 8.8±0.04 | 4.31±0.03 | 0.10±0.01 | 99.56±0.05 |
| **F5** | 452±0.42 | 8.6±0.07 | 4.20±0.02 | 0.12±0.04 | 100.13±0.13 |
| **F6** | 448±0.14 | 8.5±0.04 | 4.39±0.06 | 0.13±0.01 | 98.72±0.06 |
| **F7** | 454±0.42 | 8.0±0.07 | 4.41±0.09 | 0.15±0.05 | 98.93±0.03 |
| **F8** | 452±0.14 | 8.2±0.04 | 4.35±0.08 | 0.14±0.04 | 99.24±0.07 |
| **F9** | 450±0.14 | 8.6±0.01 | 4.34±0.02 | 0.10±0.02 | 99.35±0.08 |

**Mean±SD(n=3)**

From the above post compression parameters the tablets were found to comply with the official standards.

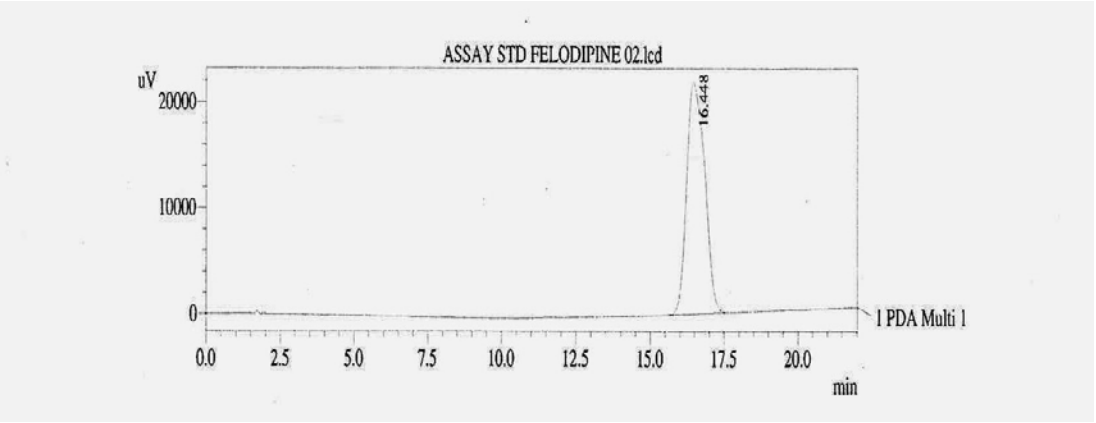



**Fig 12: Assay Chromatogram for Standard**

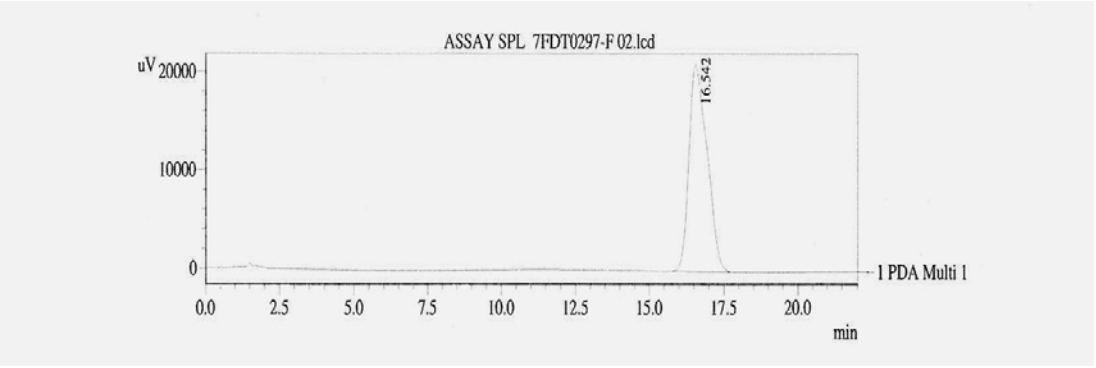



**Fig 13: Assay Chromatogram for Sample**

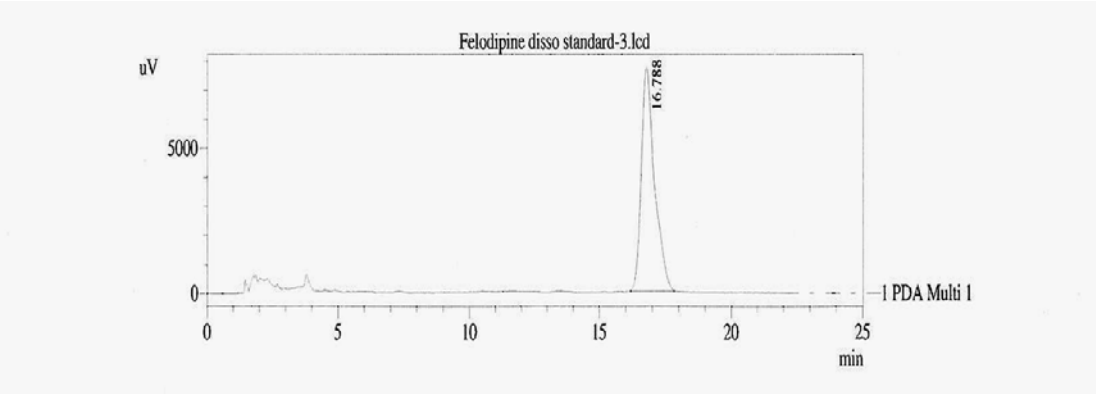



**Fig 14: Dissolution Chromatogram for Standard**

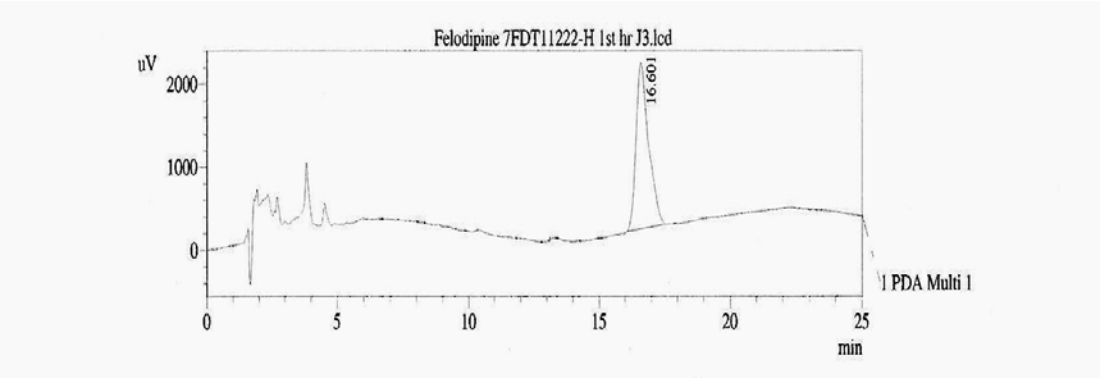



**Fig 15: Dissolution chromatogram for sample 1 hr**

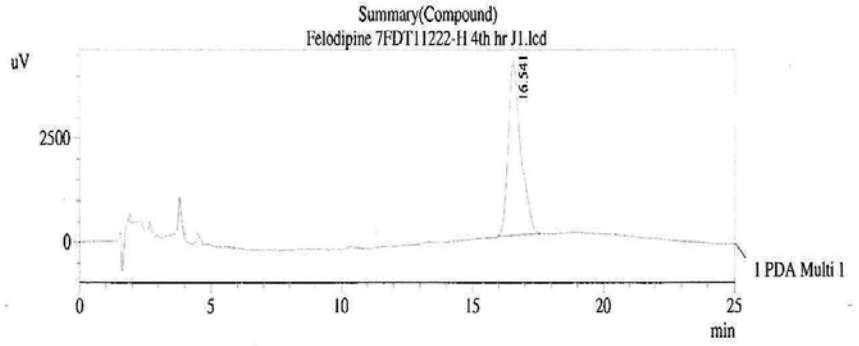



**Fig 16: Dissolution chromatogram for sample 4 hrs**

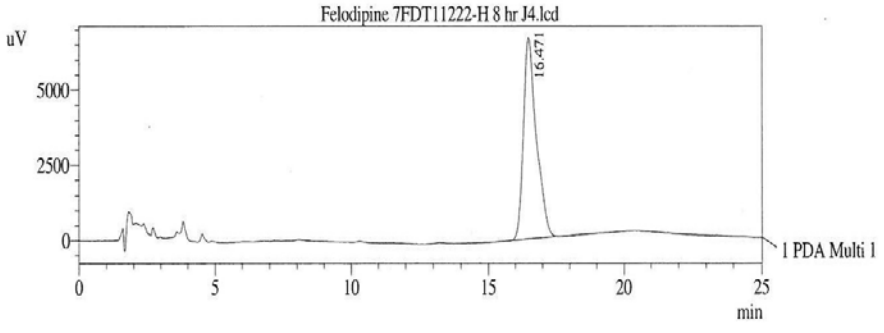



**Fig 17: Dissolution chromatogram for sample 8 hrs**

## *7.4* *Invitro* dissolution study

**Table 18: *Invitro* dissolution Profile for formulation (F3)**

| S. No | Time(hrs) | Cumulative % drug release ± SD |
|---|---|---|
| 1 | 1 | 6.23±0.23 |
| 2 | 2 | 11.15±0.42 |
| 3 | 4 | 21.32±0.24 |
| 4 | 6 | 30.57±0.45 |
| 5 | 8 | 39.78±0.51 |

All values are expressed as mean ± SD, n=3

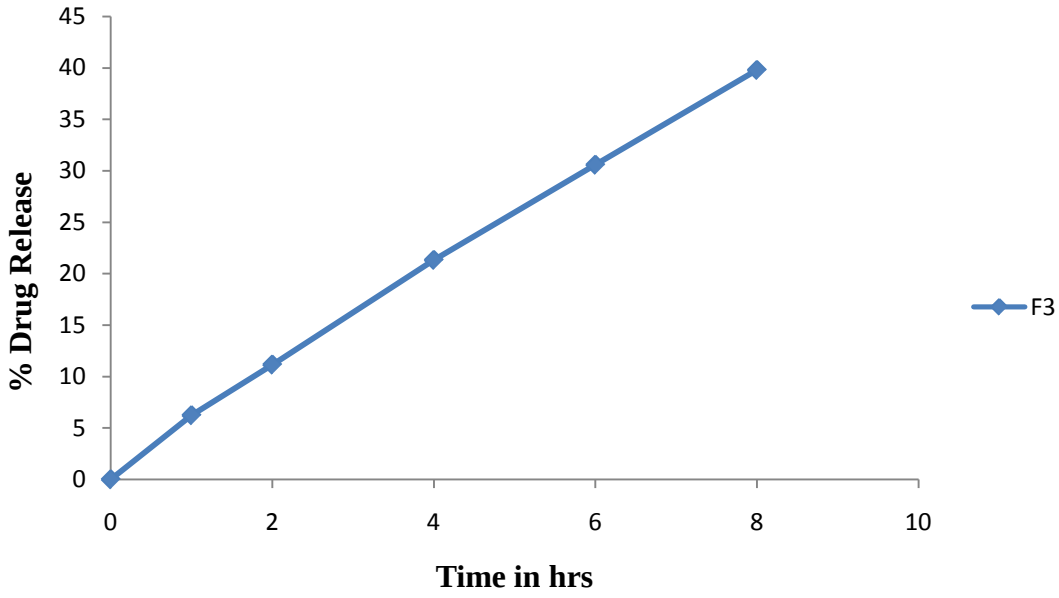



**Fig 18 : *Invitro* dissolution profile for formulation F3**

**Table 19: *Invitro* dissolution Profile for formulation (F4)**

| S.No | Time (hrs) | Cumulative % drug release ± SD |
|---|---|---|
| 1 | 1 | 10.37±0.14 |
| 2 | 2 | 16.23±0.42 |
| 3 | 4 | 27.65±0.45 |
| 4 | 6 | 39.18±0.32 |
| 5 | 8 | 53.71±0.36 |

All values are expressed as mean ± SD, n=3

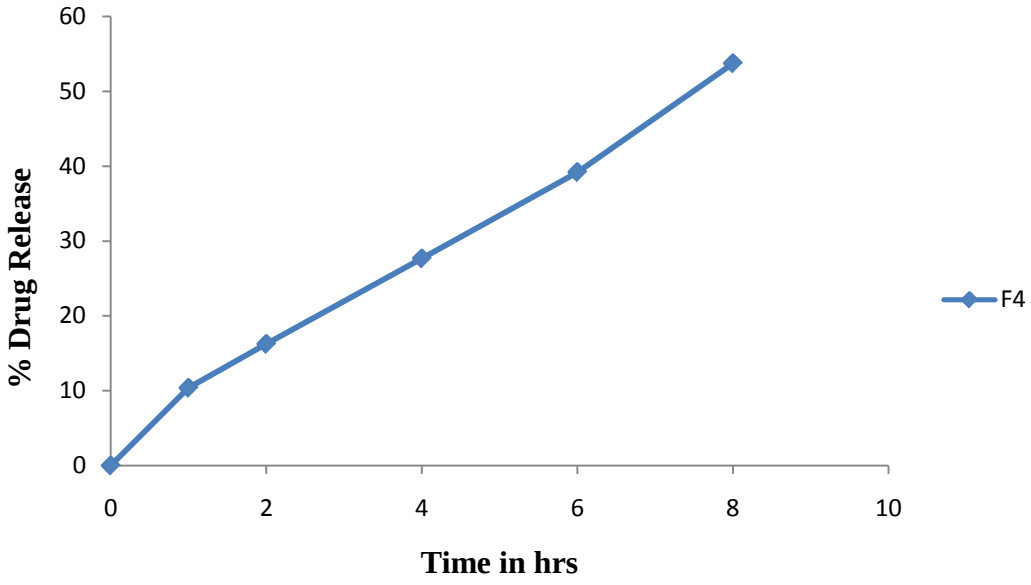



**Fig 19 : *Invitro* dissolution profile for formulation F4**

**Table 20: *Invitro* dissolution Profile for formulation (F5)**

| S.No | Time(hrs) | Cumulative % drug release ± SD |
|---|---|---|
| 1 | 1 | 14.63±0.54 |
| 2 | 2 | 20.28±0.49 |
| 3 | 4 | 33.53±0.36 |
| 4 | 6 | 46.71±0.44 |
| 5 | 8 | 60.43±0.12 |

All values are expressed as mean ± SD, n=3

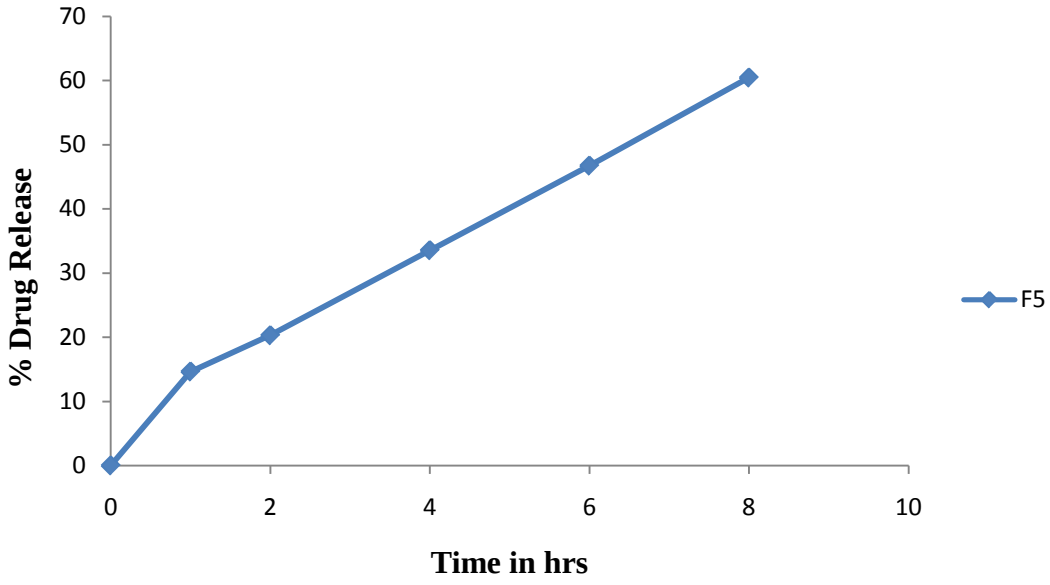



**Figure 20 : *Invitro* dissolution Profile for formulation (F5)**

**Table 21 : *Invitro* dissolution profile for formulation (F6)**

| S.No | Time(hrs) | Cumulative % drug release ± SD |
|---|---|---|
| 1 | 1 | 21.24±0.17 |
| 2 | 2 | 26.89±0.46 |
| 3 | 4 | 39.23±0.52 |
| 4 | 6 | 54.82±0.47 |
| 5 | 8 | 71.42±0.26 |

All values are expressed as mean ± SD, n=3

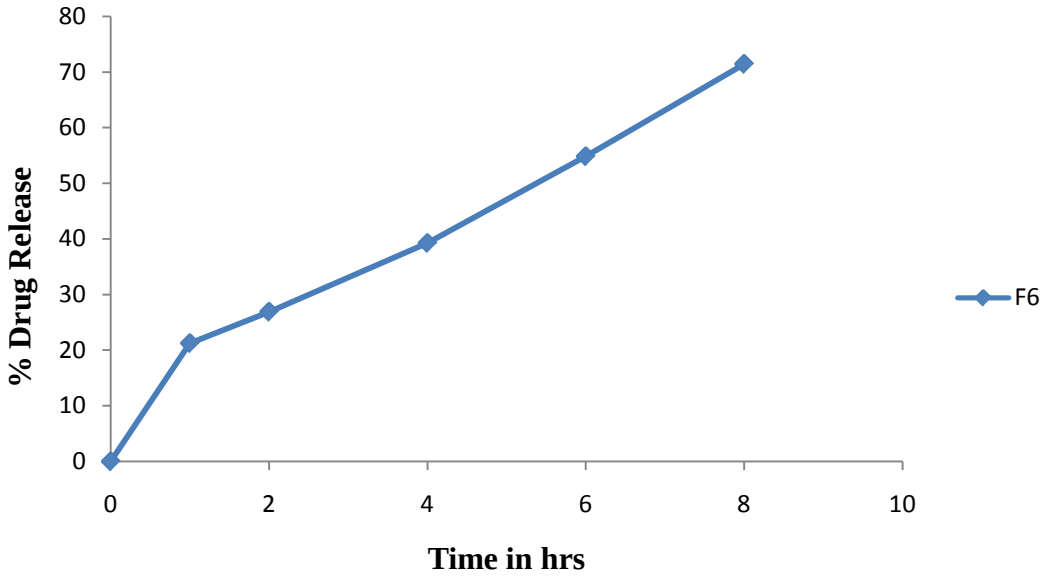



**Fig 21*: Invitro* dissolution Profile for formulation (F6)**

**Table 22: *Invitro* dissolution Profile for formulation (F7)**

| S.No | Time(hrs) | Cumulative % drug release± SD |
|---|---|---|
| 1 | 1 | 36.62±0.34 |
| 2 | 2 | 48.82±0.48 |
| 3 | 4 | 73.93±0.13 |
| 4 | 6 | 96.87±0.40 |
| 5 | 8 | - |

All values are expressed as mean ± SD, n=3

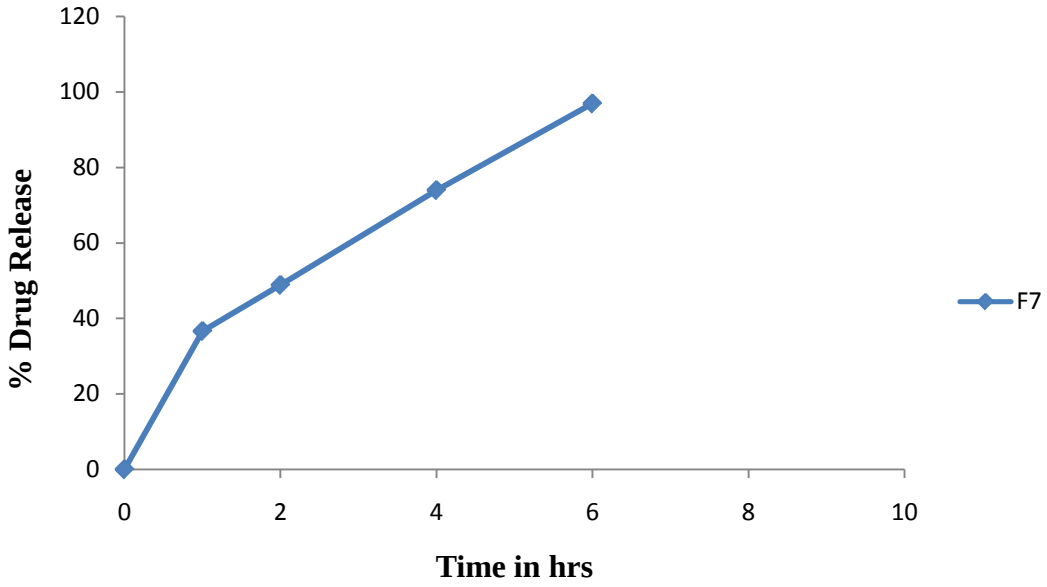



**Fig 22: *Invitro* dissolution Profile for formulation (F7)**

**Table 23*: Invitro* dissolution Profile for formulation (F8)**

| S. No | Time(hrs) | Cumulative % drug release ± SD |
|---|---|---|
| 1 | 1 | 28.86±0.40 |
| 2 | 2 | 40.27±0.24 |
| 3 | 4 | 64.69±0.28 |
| 4 | 6 | 88.72±0.32 |
| 5 | 8 | - |

All values are expressed as mean ± SD, n=3

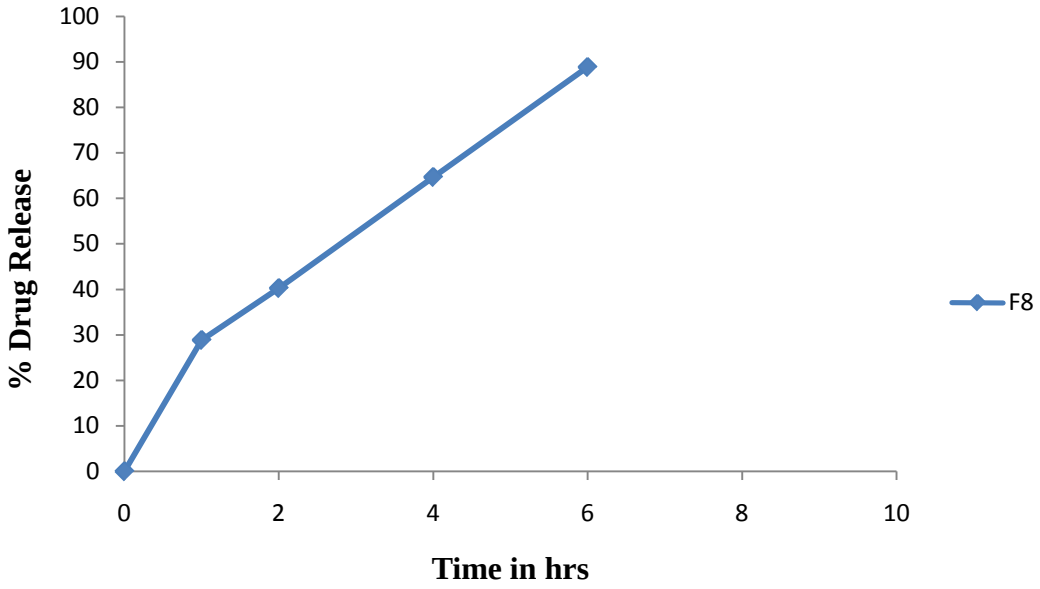



**Figure 23: *Invitro* dissolution Profile for formulation (F8)**

**Table 24: *Invitro* dissolution Profile for formulation (F9)**

| S.No | Time(hrs) | Cumulative % drug release ± SD |
|---|---|---|
| 1 | 1 | 21.5± 0.21 |
| 2 | 2 | 31.26±0.42 |
| 3 | 4 | 51.94±0.36 |
| 4 | 6 | 72.86±0.38 |
| 5 | 8 | 92.87±0.52 |

All values are expressed as mean ± SD, n=6

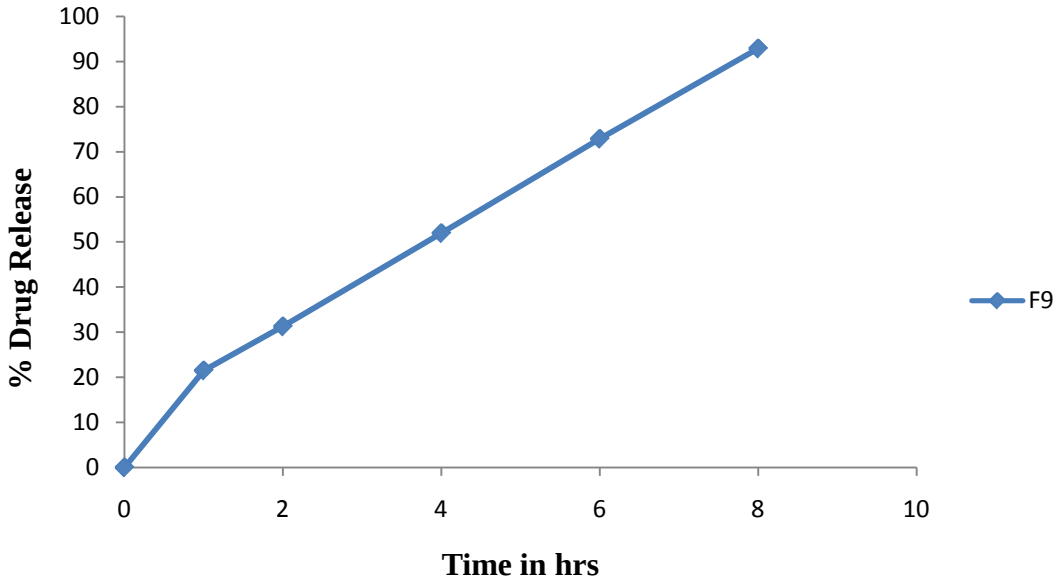



**Fig 24: *Invitro* dissolution Profile for formulation (F9)**

**Table 25: Evaluation of film Coated tablet (F9)**

| | |
|---|---|
| **Average weight(mg)** | 463.5 |
| **Hardness(kg/cm$^2$)** | 9.0 |
| **Thickness (mm)** | 4.45 |
| **Assay (%)** | 99.13 |

**Table 26: *Invitro* dissolution Profile for formulation (F9) film coated tablet**

| S.No | Time(hrs) | Cumulative % drug release ± SD |
|---|---|---|
| 1 | 1 | 20.11±0.24 |
| 2 | 2 | 30.43±0.38 |
| 3 | 4 | 51.28±0.26 |
| 4 | 6 | 72.16±0.45 |
| 5 | 8 | 92.07±0.44 |

All values are expressed as mean ± SD, n=6

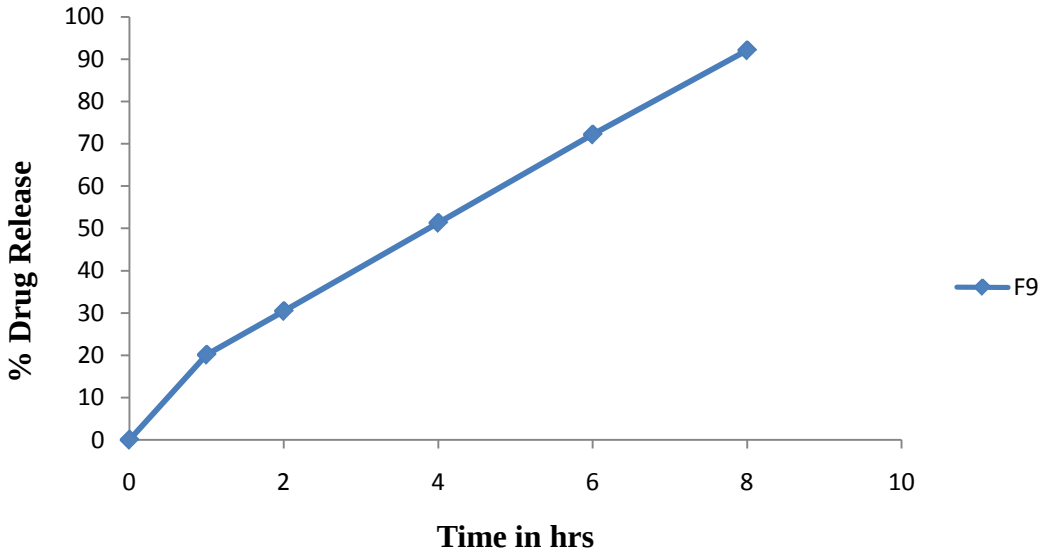



**Figure 25:*Invitro* dissolution Profile for formulation (F9) film coated tablet**

**Table 27: *Invitro* dissolution Profile for formulation (F3-F9) & Marketed product**

| Time interval (hrs) | % cumulative drug release± SD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **Marketed product** |
| 1 | 6.23± 0.23 | 10.37± 0.14 | 14.63± 0.54 | 21.24± 0.17 | 36.62± 0.34 | 28.86± 0.40 | 20.11± 0.24 | 20.93± 0.46 |
| 2 | 11.15± 0.42 | 16.23± 0.42 | 20.28± 0.49 | 26.89± 0.46 | 48.82± 0.48 | 40.27± 0.24 | 30.43± 0.38 | 31.55± 0.22 |
| 4 | 21.32± 0.24 | 27.65± 0.45 | 33.53± 0.36 | 39.23± 0.52 | 73.93± 0.13 | 64.69± 0.28 | 51.28± 0.26 | 52.48± 0.34 |
| 6 | 30.57± 0.45 | 39.18± 0.32 | 46.71± 0.44 | 54.82± 0.47 | 96.87± 0.40 | 88.72± 0.32 | 72.16± 0.45 | 73.52± 0.48 |
| 8 | 39.78± 0.51 | 53.71± 0.36 | 60.43± 0.12 | 71.42± 0.26 | - | - | 92.07± 0.44 | 93.54± 0.32 |

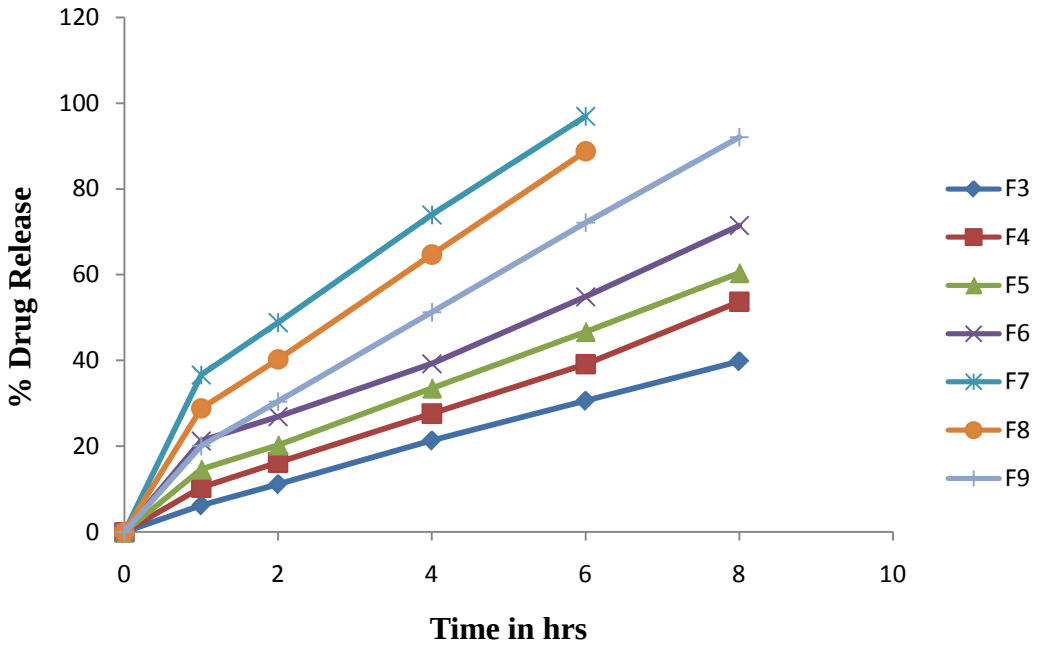



**Fig 26: Invitro dissolution profile for formulation (F3-F9)**

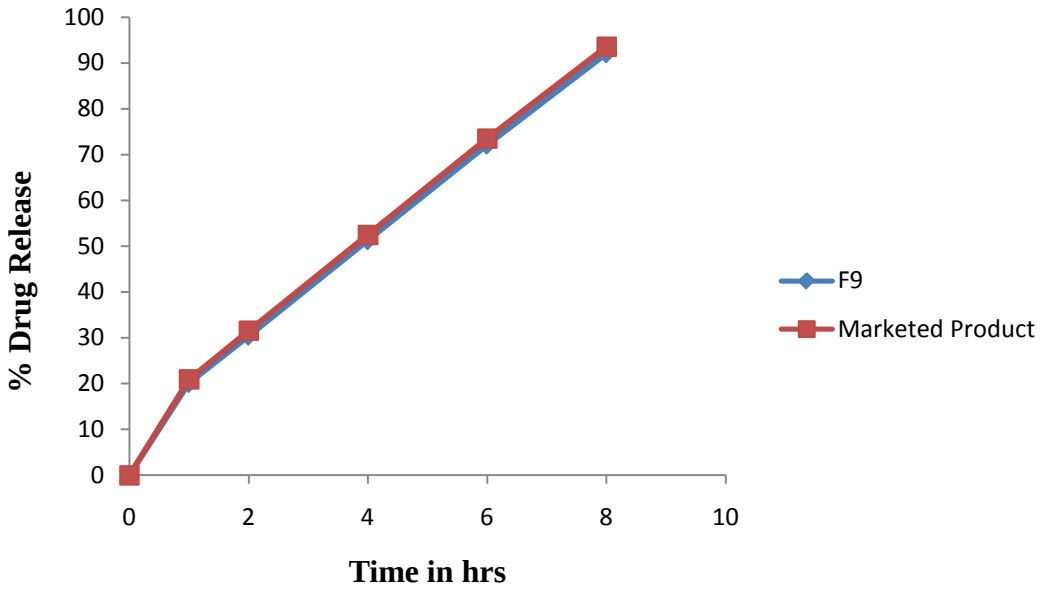



**Fig 27: Comparison of optimized formulation (F9) with Marketed product**

### *7.5 Release kinetics:*

**Table 28: Kinetic studies of matrix Tablets**

| Cumulative (%) release | Time t | Root t | Log% release | Log t | Log% remain | Release rate cum% release | 1/cum % release | Peppas log q/100 |
|---|---|---|---|---|---|---|---|---|
| 20.11 | 1 | 1.00 | 1.30 | 0.00 | 1.90 | 20.11 | 0.05 | -0.70 |
| 30.43 | 2 | 1.41 | 1.48 | 0.30 | 1.84 | 15.22 | 0.03 | -0.52 |
| 51.28 | 4 | 2.00 | 1.71 | 0.60 | 1.69 | 12.82 | 0.02 | -0.29 |
| 72.16 | 6 | 2.45 | 1.86 | 0.78 | 1.44 | 12.03 | 0.01 | -0.14 |
| 92.07 | 8 | 2.83 | 1.96 | 0.90 | 0.90 | 11.51 | 0.01 | -0.04 |

| Release kinetics | $R^2$ |
|---|---|
| Zero order | 0.989 |
| First order | 0.920 |
| Higuchi | 0.959 |
| Korsmeyers peppas | 0.992 |

**Korsmeyers peppas Equation:**

n = 0.719

### 7.5.1 Zero Order Kinetics:

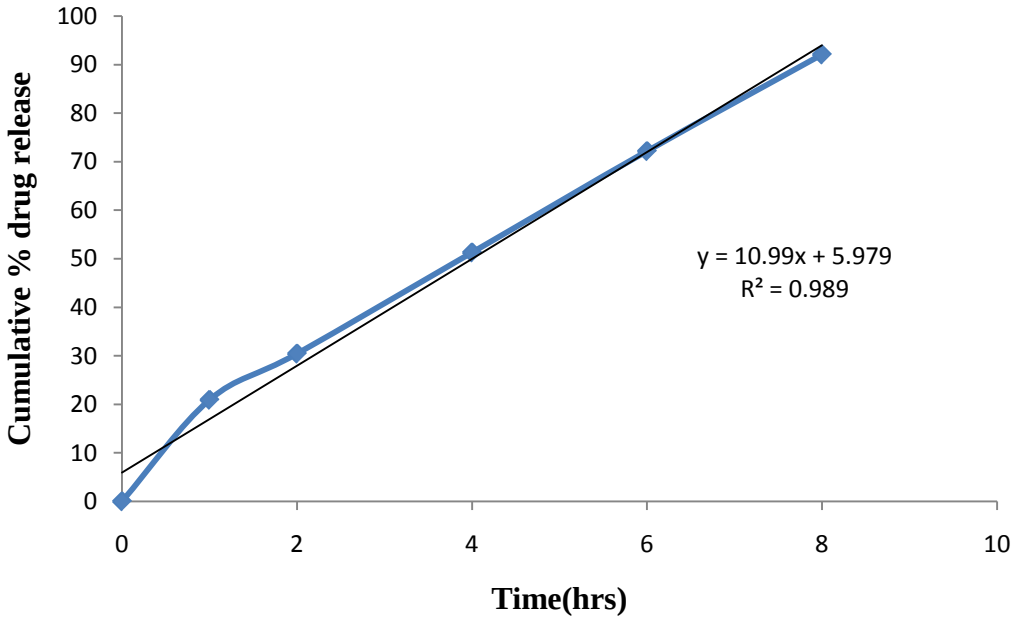



**Fig 28: Graph for the formulation F8-Zero Order Kinetics**

### 7.5.2 First order kinetics:

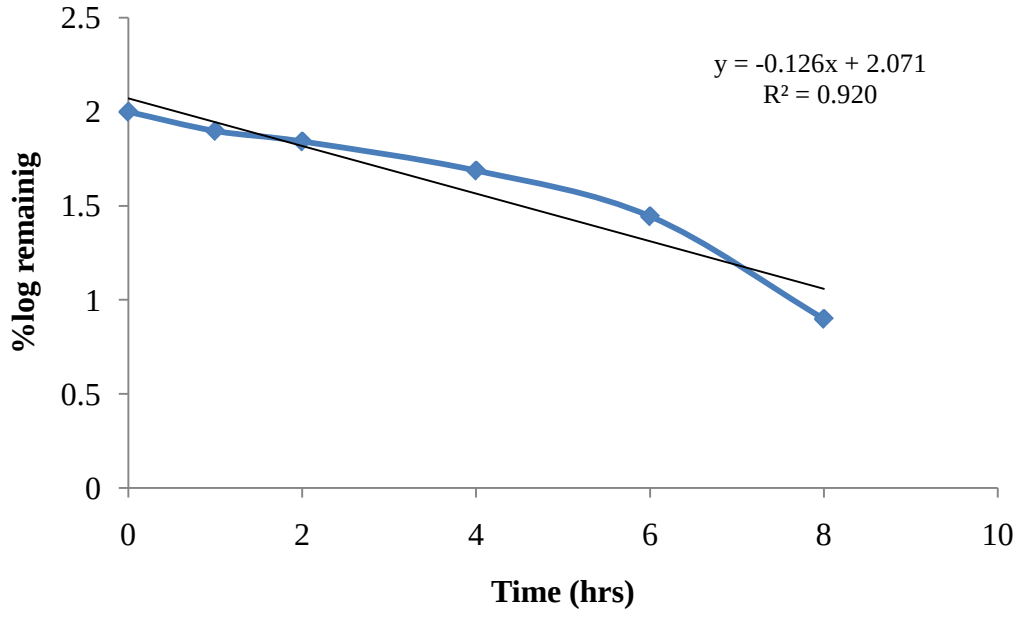



**Fig 29: Graph for the formulation F8-First Order Kinetics**

### 7.5.3 Higuchi Kinetics:

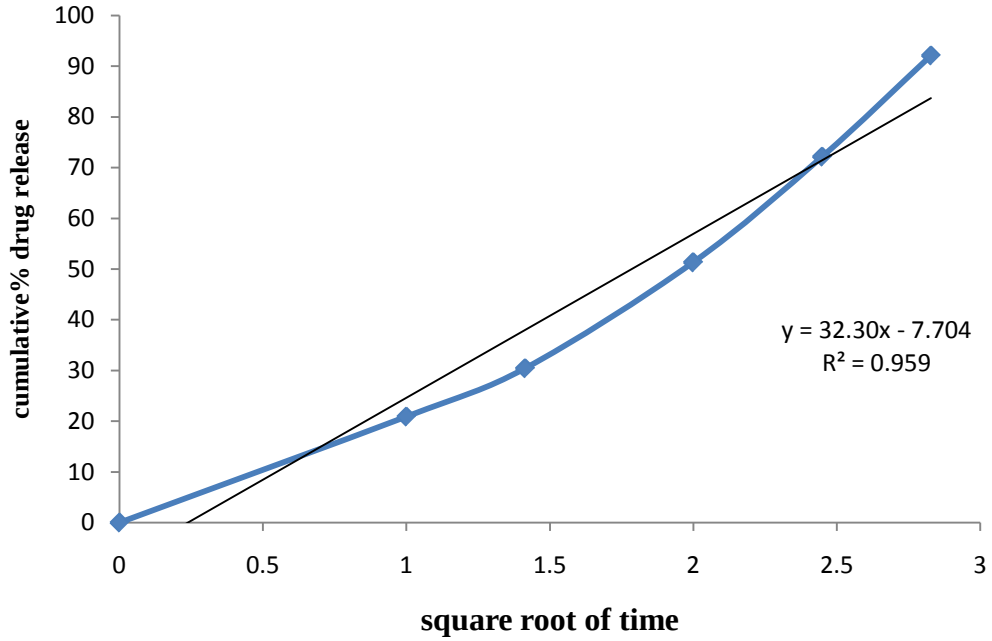



**Fig 30: Graph for the formulation F8-Higuchi model**

### 7.5.4 Korsmeyers Peppas Model:

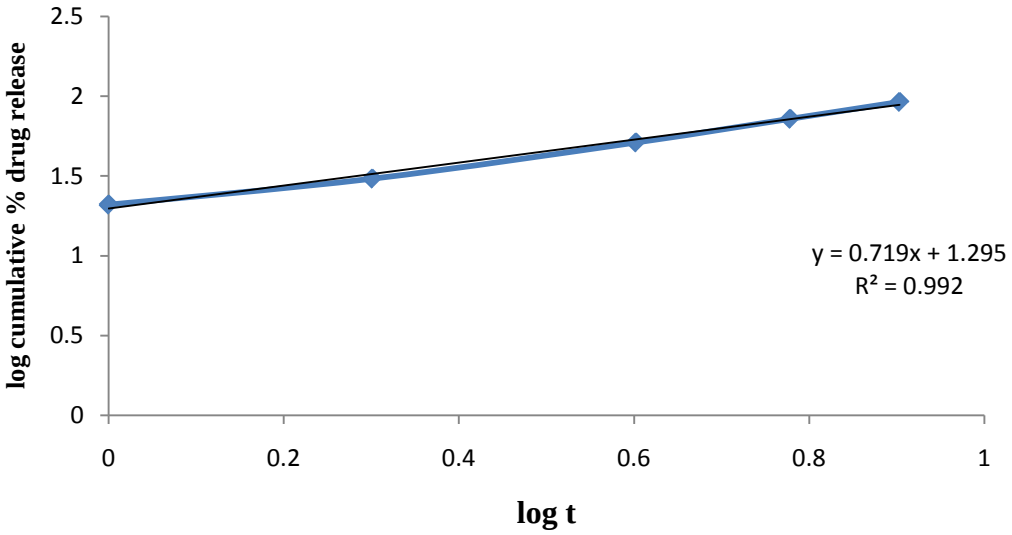



**Fig 31: Graph for the formulation F8- Korsmeyers Peppas model**

## 7.6 Similarity Factor and Differential Factor:

**Table 29: Comparision between Test and Reference Product**

| S.No | Time(hrs) | Cumulative % drug release ± SD (test) | Cumulative % drug release ± SD (reference) |
|---|---|---|---|
| **1** | 1 | 20.11±0.24 | 20.93± 0.46 |
| **2** | 2 | 30.43±0.38 | 31.55± 0.22 |
| **3** | 4 | 51.28±0.26 | 52.48± 0.34 |
| **4** | 6 | 72.16±0.45 | 73.52± 0.48 |
| **5** | 8 | 92.07±0.44 | 93.54± 0.32 |

**Table 30: Similarity Factor and Differential Factor Calculation**

| | |
|---|---|
| **Differential Factor - F1 [ Acceptance Criteria : 0 -15]** | 2.19 |
| **Similarity Factor - F2 [ Acceptance Criteria : 50-100]** | 90.16 |

## 7.7 Stability Studies:

**Table 31: Accelerated Stability Study**

**Storage conditions at 40°C ± 2°C /75 % ± 5%RH**

| Parameters | Initial | 1st Month | 2nd Month | 3rd Month |
|---|---|---|---|---|
| **Description** | White colour, circular shape, slightly biconvex, film coated tablet | Complies | Complies | Complies |
| **Average weight (mg)** | 463.5 | 463.5 | 463.4 | 463.2 |
| **Thickness (mm)** | 4.45 | 4.45 | 4.44 | 4.44 |
| **Hardness ($kg/cm^2$)** | 9 | 9 | 8.9 | 8.9 |
| **Assay (%)** | 99.13 | 99.08 | 99.02 | 98.93 |
| **Dissolution** | 92.07 | 92.01 | 91.89 | 91.76 |

# Discussion

**Preformulation:**

The experimental work started with the raw material analysis of felodipine as per USP, the physical properties such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose values were depicted in the **Table: 16**

**Calibration curve:**

The calibration curve of Felodipine was prepared in 0.1N HCL at determined wavelength at 241nm. The $r^2$ and slope were found to be 0.9946 and 0.0628.The results were shown in **Table 15 and Fig: 6**

**FT-IR Studies:**

The IR spectra of pure drug showed sharp peaks at 1689$cm^{-1}$ for C=O Ester,1643 $cm^{-1}$ for NH Bending, 1642,1496 $cm^{-1}$ for -C=C Stretching,1099 $cm^{-1}$ for –C-O-C, 790$cm^{-1}$for Benzene ring Stretching,567$cm^{-1}$for C-Cl for Stretching. These peaks were found to be prominent in the spectra of physical mixtures containing the drug and excipients. This indicates there was no interaction between drug and excipients shown in the **Fig: 7-13.**

**Evaluation of Physical Mixture:**

Bulk density, Tapped density, Carr's index, &Hausner's ratio, Angle of repose were evaluated for the prepared blend.

Formulations blend F1 and F2, the angle of repose was found to be 58.3 and 62.8. It shows very poor flow property because diluent and disintegrant concentration was low to their average weight. Bulk density, Tapped density, Carr's index and Hausner's ratio was not within the limits. Carr's index was found to be 29.7 and 27.2. Hausner's ratio was found to be 1.41 and 1.38.From this it indicates that the

formulation F1 and F2 have poor flow property and also not suitable for compression.

From the formulations F3 to F9, to improve the flow property, diluent and disintegration concentration was increased, it shows good flow property. The angle of repose was found to be in the range 25.1˚ to 31.6˚.Compressibility index was carried out, it found between14.2 to 18.1, indicating the powder blend has the required flow property for compression. Hausner's ratio was calculated for the blend, it was found to be 1.16-1.22. The results showed in the **Table: 16**

**Evaluation of Core Tablet:**

The results were shown in the **Table: 17.** The hardness of tablets of each batch ranged between 8 to 9 kg/cm2, this ensures good handling characteristics of all batches. Thickness of all the formulation was found to be in the range 4.20mm to 4.40mm. All the formulations were found to be in the range 0.08% to 0.15%.The percentage of drug content for F3 to F9 was found to be 98.64% to 100.13%, it complies with official specifications.

**Effect of HPMC K100 and HPMC K4M on drug release:**

All the formulations were prepared by dry granulation technique. Different formulations were developed using different concentration of polymer. Basically, HPMC is a hydrophilic polymer which controls the release rate of the drug for the extended period of time. For the formulation F3 containing 17% of HPMCK100 and 4% of HPMC K4M, the release from the formulations were found to be 39% at the end of $8^{th}$ hour which shows the release was not within the USP specification limit. As the polymer concentration was high, the drug release shows poor. The results were shown in the **Table 18 and Fig 19.**

For the formulation F4 the polymer concentration was reduced to 11% of HPMC K100 and 3% of HPMC K4M, the drug release were found to be 53.71% which are not within the specified limits, but the release was improved compared to

F3,the concentration of polymer was high which provides the slow release of drug, it was further reduced. The results were shown in the **Table19 and Fig 20.**

Formulation F5 HPMC K100 was reduced to 6% and HPMC K4M was kept at same concentration, the release was found to be60%, because HPMC K4M, a high viscosity grade was more, it was reduced to the next formulation. The results were shown in the **Table 20 and Fig 21.**

Formulations F6, the polymer was reduced to 4.5% of HPMC K100 and 2.5% of HPMC K4M shows the release 72% at the end of 8 hours which was not within the USP limits. The results were shown in the **Table 21 and Fig 22.**

Hence to meet the required release profile, polymer concentration was further reduced for the formulation F7 (1.5% of HPMC K100 and 1% of HPMC K4M), 97% of the drug was released at the end of 6 hours. The results show the drug was not released for extended period of time because of their low polymer concentration. Therefore, the polymer concentration was increased for next trial. The results were shown in the **Table 22and Fig 23.**

Formulation F8 containing 2.5% of HPMC K100 and 1.5% of HPMC K4M, which shows 89% of the drug was released at the end of 6 hours. Furthermore, the polymer concentration was increased to the next trial. The results were shown in the **Table 23 and Fig 24.**

Finally, the release from the formulation F9 containing 3% of HPMC K100 and 2 % of HPMC K4M at $1^{st}$,$4^{th}$,$8^{th}$ was found to be 21.5%, 51.94%, 92.87% which was within the USP limits. The results were shown in the **Table 24 and Fig 25.**

When the concentration of polymer was increased, the drug release was found to be decreased. The type and concentration of polymer influenced the rate and release of the drug. Therefore, from formulations F3 to F9 different concentration of HPMC K100 and HPMC K4M showed different release profiles, of these formulations F9was observed to be followed USP specifications for extended release tablets.

**Interpretation of Dissolution Profile:**

The results of dissolution studies indicate that the release was influenced by the viscosity grade of polymers. The polymer HPMC K100, HPMC K4M had a retarding effect with high concentration. When the polymer concentration is high, the drug release was found to be slow. Once there is a sufficient polymer concentration is achieved in the core of the tablet or in the matrix system, upon dissolution a uniform layer is formed to protect the drug release immediately into the dissolution medium. According to this only the formulation F9 followed the desired release profile upto $8^{th}$ hour, as per the requirement of US Pharmacopoeia.

**Evaluation of film coated tablet:**

The optimized formulation F9 was observed. The results were shown in the **Table 26 and Fig 26.** The thickness was found to be in the range 4.45mm. The hardness was found to be 9 $kg/cm^2$. The percentage of drug content was 99.13%.Optimized formulation F9, the drug release was found to be 20.11%, 51.28% and 92.07 % at the end of $1^{st}$,$4^{th}$ and $8^{th}$ hour which was within the USP limit. Formulation F9 shows the similar release profile to marketed product.

**Release kinetic study for optimized matrix tablet:**

Dissolution data of the optimized formulation was fitted to various kinetic model (zero order, first order, Higuchi and korsmeyers peppas) in order to describe the drug release profile. The plot of cumulative percentage drug release as a function of time indicates that none of the formulation follows first order or Higuchi Kinetics **(Table: 28)** the line of best fit obtained was zero order release kinetics ($R^2$=0.989) and Korsmeyers Peppas model, the drug release data further analyzed for curve fitting and the results (n=0.719) confirmed that the formulation follows non–fickian (anomalous) diffusion kinetics.

**Comparision between Optimized batch and Marketed product:**

The optimized formulation F9 was compared to the marketed product. In optimized formulation, the drug release was found to be20.11%, 51.28%, 92.07% at the end of $1^{st}$,$4^{th}$ and $8^{th}$ hour was seemed to be close to the marketed product, the drug release was found to be 20.93%, 52.48% and 93.52%. Similarity factor( $f_2$) and dissimilarity factor($f_1$) was calculated between F9 and marketed product. Differential factor ($f_1$) and Similarity factor ($f_2$) was found to be 2.19 and 90.16, which shows similar release profile to the marketed product. The results were shown in the **Table 30.**

**Stability batch:**

Stability studies were conducted for the formulations F9. The stability study was performed at 40°C /75 % RH/ 3 months. The tablets were analyzed for appearance, average weight, thickness, hardness, drug content and *in vitro* drug release. The overall results showed that the formulation is stable at the above mentioned Storage conditions the results were depicted in **Table: 31**

# 8. Summary

In the present study an attempt was made to prepare Felodipine Extended release tablet for the treatment of hypertension.

**Chapter 1**- begins with a general introduction presenting an overview of about extended release drug delivery systems. In the part of introduction the advantages, disadvantages, mechanism of extended release systems and matrix tablets were discussed thoroughly.

**Chapter2**- described the literature related to this work was surveyed and a brief discussion had been given on each literature.

**Chapter 3 -** detailed the aim and objective of the present study.

**Chapter 4**- described the plan of the work.

**Chapter 5 -**gives information on the selection of drugs and excipients; thereby felodipine is suitable candidate for extended release dosage form.

**Chapter 6-**deals with the materials and methods used in the present study was given. This chapter covers the details of the experimental methods including evaluation of the core and film tablets, evaluation of physical mixture and also about release kinetics.

**Chapter 7-** Includes the results and detailed discussion of all the formulations, all the qualitative and quantitative parameters were analyzed and tabulated. The drug excipient compatibility study was done and found to have no interactions.

Pre-compression parameters of the prepared tablets (Bulk density, Tapped density, Carrs index and Angle of repose) are in the range of given in official standard, indicates that the physical mixture were found to be free flowing. *Invitro* dissolution studies were done for Felodipine Extended release tablet prepared with different concentration of polymer HPMC K100 low viscosity grade and HPMC

K4M high viscosity grade. Formulation F9 was found to be 92.07% drug release at the end of $8^{th}$ hours which was within the USP limits.

The kinetic of drug release for formulation F9 was calculated and plotted. The formulation F9 follows zero order release kinetics and the drug release mechanism was found to be non-fickian (anomalous) diffusion. The optimized formulation was compared with marketed product and showed similar release profile.

The optimized tablets F9 were selected for stability studies were carried out according to ICH guidelines at $40^{\circ}C$ /75 % RH for a specific time period indicated that the physical parameters and drug release characteristics were not altered significantly showing good stability on storage.

# 9. Conclusion

Felodipine is widely used an anti hypertensive agent. It is formulated as an extended release tablet, which shows better patient compliance and reduces side effects. Based on various studies carried out we have arrived at following conclusions.

Extended release matrix tablet of Felodipine 10mg prepared by dry granulation technique. Various polymers with various concentrations were developed and evaluated. The formulation containing 3% of HPMC K100 and 2% of HPMC K4M (F9 batch) followed the desired release profile and selected for further studies. The optimized formulation follows zero order release pattern and the drug release mechanism was non-fickian (anomalous transfer).The optimized formulation F9 and the marketed formulation were found to have a similar *invitro* release profile, which is confirmed by $f_1$ *and* $f_2$ values.

Therefore, erosion and diffusion mechanism found to be responsible for extended release of felodipine from formulated matrix tablet. The formulation (F9) found to be stable under accelerated conditions for 3 months with respect to physical characteristics and drug content. However, the *in vivo* pharmacokinetic studies are required to confirm these results.

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